ASSOCIATION OF CARDIOVASCULAR RISK FACTORS WITH INTRAOCULAR PRESSURE AND PRIMARY OPEN-ANGLE GLAUCOMA

by
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ABSTRACT

Glaucoma is a disease with characteristic optic nerve damage and vision loss. It is the leading cause of irreversible blindness affecting more than 60 million people worldwide. Glaucoma affects the quality of life in older populations and has significant public health and economic consequences for society, making it a critical public health problem. The established risk factors for the development of open-angle glaucoma (POAG), the most common type of glaucoma, are mostly non-modifiable such as age, family history, gender, race, myopia and other anatomical eye characteristics. Elevated IOP is the only modifiable and key determinant of POAG. Reducing IOP levels decreases the incidence and progression of glaucoma compared with no treatment, even in normal-tension glaucoma.

Traditional cardiovascular risk factors (hypertension, diabetes, body mass index) were suggested to influence IOP and the development of POAG. However, previous literatures were limited by cross-sectional design, small sample size and inconsistent results. The main objective of this study is to access the longitudinal association of cardiovascular risk factors with IOP trajectories, and to quantitatively synthesize the association between these risk factors and the risk of POAG.

First, we conducted a systematic review of the available literature on the association between blood pressure levels and hypertension with primary open-angle glaucoma and intraocular pressure endpoints. Sixty observational studies were eligible and included in the

final meta-analysis. High blood pressure was associated with increased IOP and higher risk of POAG.

Second, we conducted another systematic review of the available literature on the association of diabetes and blood glucose levels with glaucoma, intraocular pressure (IOP) and ocular hypertension in the general population. Forty-seven studies including 2,981,342 individuals from 16 countries were included in the final meta-analysis. Diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP.

Third, we conducted a cross-sectional analysis of 3,299 adults from 2005-2008 NHANES, to investigated the association between diabetes, pre-diabetes, metabolic syndrome and its components and the levels of fasting glucose, HbA1c and HOMA-IR with the prevalence of glaucoma. Diabetes was associated with higher risk of glaucoma. We also found hockey-stick shaped associations between biomarkers of glucose metabolisms and the prevalence of glaucoma.

Fourth, we examined the longitudinal association between age and IOP in a prospective cohort study of 274,064 adult men and women who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. IOP was inversely associated with age in this population, and the association was stronger in men compared with women.

Finally, we examine the longitudinal and cross-sectional associations between body mass index (BMI), waist circumference, percent fat mass and IOP in the same population of 274,064 Korean men and women. All body adiposity markers were positively associated with increased IOP in both longitudinal and cross-sectional fashion, and the association was more evident in central obesity represented by waist circumference.

In conclusion, hypertension and diabetes are risk factors for POAG and elevated IOP in the general population. IOP decreased over time with age in Korean adults, and baseline and change in body adiposity are risk markers for elevated IOP in the Korean adults.

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which I can focus on work. As for Xiaojin, he has given up so much to make my career a priority in our lives, and has seen me through the ups and downs of the entire process. He is the best friend, soul mate, life companion, and the most powerful backing of mine. As for Xuanyuan, this marvelous creature completely changed my life. His smile brightens up my mood all the time and his every little bit growth and progress makes me blissful. He not only reminds me of the importance to cherish every moment, as the fast growth signals lapse of time, but also the value and love of family, the greatest gift from life that I will always strive for. To them, I dedicate this thesis.

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CHAPTER 1

INTRODUCTION

ANATOMY AND PHYSIOLOGICAL DETERMINANTS OF GLAUCOMA AND INTRAOCULAR PRESSURE (IOP)

Aqueous humor, the fluid that fills the front of the eye, is produced by the ciliary body within the posterior chamber of the eye and flows through the pupil into the anterior chamber. Aqueous humor exits the eye by filtering through the trabecular meshwork into the Canal of Schlemm and returns back to the blood circulation. The IOP is maintained by this steady state of aqueous humor production and outflow. Inadequate outflow or overproduction of inflow can result in increased intraocular pressure (IOP) and vision loss. Glaucoma is primarily a disorder of aqueous humor physiology. With prolonged high IOP, the ganglion cells are injured resulting in gradual vision loss.

GLAUCOMA EPIDEMIOLOGY

Glaucoma is a disease with characteristic optic nerve damage and vision loss. It is responsible for 14% of blindness globally,[1] and is the second leading cause of blindness in the United States (US). Primary open-angle glaucoma (POAG), which accounts for at least half of all glaucoma cases, affects more than 2.2 million persons in the US, and this number is projected to increase to 3.4 million in 2020.[2] Among US Whites, POAG is present in 0.3 – 4.0 % of people aged over 40. In Asian populations, POAG is present in 0.5 to 2.6% of the people aged over 40.[3] Other types of glaucoma include angle-closure glaucoma (ACG), congenital glaucoma and secondary glaucoma. About 10% of all individuals with glaucoma are estimated to be blind in one or both eyes.[4] Currently glaucoma is not curable, and vision lost cannot be regained.[5]

RISK FACTORS FOR GLAUCOMA

Age: Population-based studies consistently show an exponential rise in the prevalence and incidence rates with increasing age. In the Barbados Eye Study[6] and the Rotterdam study,[7] there was a 4% and a 6% increased risk of developing POAG with each year of age increase, respectively. In the Visual Impairment Project in Australia, subjects aged 70–79 years at baseline had a 12-fold increased 5-year risk of developing POAG compared to subjects aged 40–49 years old.[8]

Race: In general, the prevalence of POAG is highest in African American populations; intermediate in non-Hispanic Whites, Hispanics, and southern Asian populations (Singapore Chinese, Indian); and lowest in northern Asian populations.[9]

Genetic factors: Family history of glaucoma is an important risk factor. Having a first-degree relative with glaucoma has been consistently associated with an increased risk for POAG in prevalence surveys, and it is estimated that siblings of affected individuals have nearly an 8-fold risk of POAG when compared to siblings of unaffected individuals.[7,10]

CVD risk factors: Cardiovscular diseases, such as diabetes and hypertension, can cause microvascular damage and may affect vascular autoregulation of the retina and optic nerve.[11] Vascular damage can reduce blood flow and impair oxygen diffusion. Endothelial cell injury and dysfunction can reduce the autoregulatory capacity to protect against fluctuations of IOP, which could lead to relative hypoxia and to damage of the optic nerve head and of the retinal nerve fiber layer.[12]

Intraocular pressure (IOP): Elevated IOP level is a major risk factor for the development and progression of POAG, and lowering the IOP in patients suffering from POAG slows up the disease progression[13]. IOP is also an important consideration for diagnosis of glaucoma, as high

IOP damages the sensitive optic nerve and results in vision loss[14]. However, there is no threshold at which the IOP value is defined as dangerous, as people have different susceptibility and vulnerability of the optic nerve head to a particular IOP level[9]. In addition, there is a racial difference in the degree to which elevated IOP causes POAG. Only 5.4% of whites with ocular hypertension (IOP>21 mmHg) progress to POAG, while 18.1% of blacks with ocular hypertension progress to POAG.[15]

IOP EPIDEMIOLOGY

Average IOP varies with different ethnic groups. The mean IOP (± standard deviation [SD]) value in the general population in US is approximately 15.5 ± 2.57 mm Hg, following a Gaussian distribution[16]. Normal intraocular pressure is considered between 10 mmHg and 21 mmHg. An IOP >21 mmHg is often referred to as ocular hypertension[3].

RISK FACTORS FOR IOP

Age: Age is considered a significant factor for progression of intraocular pressure (IOP) and incidence of ocular hypertension (OHT). However, the direction of correlation is not consistent throughout previous population-based studies. In studies composed of Caucasians, blacks or Irish populations, a positive correlation between increasing age and IOP is reported[17–23]. In contrast, an inverse relationship of age and IOP is generally reported in Asian populations. IOP is found to decrease with age in cross-sectional studies and one longitudinal study in Japan[24–27].

Blood pressure: Several population based studies have consistently reported cross-sectional and longitudinal associations between increased systolic or diastolic blood pressure

with higher IOP[28–31]. The positive correlation between systolic blood pressure (SBP), diastolic blood pressure (DBP) and IOP observed in both healthy individuals and OAG patients also appears to be present across all races. However, the actual change in IOP with increasing BP is relatively small. In cross-sectional studies, each 10 mm Hg increment in SBP leads to a mean of 0.23 to 0.32 mm Hg rise in IOP, and each 10mm Hg increment in DBP leads to a mean of 0.19 to 0.55 mm Hg rise in IOP. In longitudinal analysis of Beaver Dam Study, each 10 mm Hg increase in SBP from baseline leads to a 0.21 mm Hg rice in IOP over a 5-year interval. If we assume that the mean IOP at baseline is 15 mm Hg, then the change is about 1.4% over a 5 year interval.

Central corneal thickness: Measurement of IOP is subject to the influence of central corneal thickness. The general procedures of IOP measurement require placing the tip of tonometry equipment against the cornea; the IOP is read by configure the appropriate amount of force to flattening or indenting the cornea. Thee principle is that IOP is proportional to the force required to flatten a defined area of cornea. Thin cornea leads to underestimation of true IOP while thick cornea leads to falsely higher pressure readings[3]

Diabetes: Several cross-sectional studies have documented that populations with high prevalence of diabetes or raised blood glucose level have an increased risk of elevated IOP[32,33]. One study also found that a number of metabolic abnormalities related to insulin resistance were associated with elevated IOP[34]. In addition, several cross-sectional studies have documented a correlation between elevated blood glucose or HbA1c levels and raised IOP in diabetic patients[11,29,35,36].

Obesity: Previous cross-sectional studies have consistently shown that obesity and increasing BMI are risk factors for elevated IOP[19,37–40]. Interestingly, although BMI is a risk

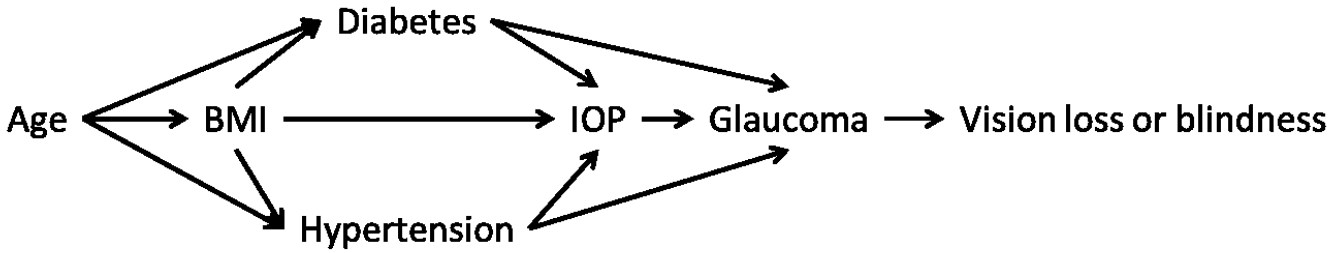
factor for higher IOP, BMI may have a U-shaped association with glaucoma[32]. The U shape could be related to the fact that underweight individuals may be more likely to have chronic or infectious disease, which may affect their susceptibility to ocular hypertension. Potential mechanisms include excess intraorbital fat tissue, increased episcleral venous pressure, and increased blood viscosity with increased outflow resistance of episcleral veins. These factors could result in decreased in outflow facility. Another study suggested that the breath holding and thorax compression while tonometry is performed at the slitlamp on obese patients may cause transitory elevations of IOP, thus increase IOP readings using Goldmann tonometer[41].

SIGNIFICANCE

Glaucoma accounts for 9% to 12% of all cases of blindness in the U.S[5]. High IOP is the most important risk factor for primary pen-angle glaucoma, which accounts for >50% glaucoma cases. Since open-angle glaucoma is a chronic condition, it must be monitored for life, which makes IOP a key component of regular eye examination. Ocular hypertension is common in the elderly. About 2% of the population ages 40-50 and 8% over 70 have ocular hypertension. The prevention of ocular hypertension and IOP control have public health significance in reducing incidence and progression of glaucoma. However, the underlying mechanism for cardiovascular risk factors to impact ocular pressure remains elusive. Our study will delve into both traditional and non-traditional CVD risk factors and explore the correlation between those risk factors and the progression of IOP. Both identification and summation of the CVD risk factors need to be characterized to reach an assessment of people at risk of developing ocular hypertension and to facilitate targeted intervention toward glaucoma and vision loss.

INNOVATION OF THIS THESIS

Figure 1. Conceptual framework for CVD risk factors with glaucoma and IOP



Identifying potential modifiable risk factors can has important implication in glaucoma prevention and improvement of prognosis. However, current studies on the CVD risk factors were limited by cross-sectional design, small sample size, or highly selective population. The cross-sectional studies were incapable of establishing temporality, while the few longitudinal studies reported conflicting results. With regard to the gap in previous literatures, the objective of this thesis is to first summarize and quantitatively synthesize available literature on the association of CVD risk factors with the risk of glaucoma and IOP, and then investigate the longitudinal association of CVD risk factors with IOP trajectories using the Kangbuk Samsung cohort study.

Our study has several strengths compared with previous studies. Our cohort study is by far the largest population-based cohort study evaluating the longitudinal association between CVD risk factors and IOP. Our longitudinal design enables us to be less affected by biases commonly seen in cross-sectional studies. We also adopted three-level hierarchical approach to appropriately account for correlations between eyes and between visits for each participant.

In the following chapters, we would like to individually evaluate the association of CVD risk factors, including hypertension, diabetes, age and BMI, with glaucoma and IOP endpoints. Our hypothesis is that diabetes, hypertension and BMI are positively associated with

risk for glaucoma and IOP. (**Figure 1**) In addition, we hypothesize that IOP may decrease with age, which was suggested in most of the previous cross-sectional studies based on Asian population. Our study contributes to the understanding of IOP and glaucoma mechanism, and has clinical implication on the treatment of glaucoma through IOP reduction.

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CHAPTER 2

THE ASSOCIATION OF BLOOD PRESSURE AND PRIMARY OPEN-ANGLE GLAUCOMA: A META-ANALYSIS

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis of the association between blood pressure levels and hypertension with primary open-angle glaucoma and intraocular pressure endpoints.

Clinical Relevance: Blood pressure is a potentially modifiable risk factor that may contribute to intraocular hypertension and glaucoma risk, but individual studies of the association between hypertension and glaucoma have been inconsistent.

Design: Systematic review with quantitative meta-analysis.

Methods: Studies were identified by searching the PubMed and EMBASE databases. Inverse-variance weighted random-effects models were used to summarize relative risks. Subgroup analyses and meta-regression were used to explore potential sources of heterogeneity across studies.

Results: Sixty observational studies were included. The pooled relative risk for primary open-angle glaucoma comparing patients with hypertension to those without hypertension was 1.16 (95% CI= 1.05-1.28), with modest heterogeneity across studies (I^2 34.5%). Virtually all studies reported a positive association between blood pressure and intraocular pressure. The pooled average increase in IOP associated with a 10 mmHg increase in SBP was 0.26 mmHg (95% CI 0.23 – 0.28, I^2 30.7%), and the average increase associated with a 5 mmHg increase in DBP was 0.17 mmHg (95% CI 0.11 – 0.23, I^2 90.5%).

Conclusions: In this meta-analysis, hypertension was associated with increased intraocular pressure. The association between hypertension with primary open-angle glaucoma was stronger in cross-sectional compared with case-control and longitudinal studies. Our findings

support a role of increased blood pressure in elevated intraocular pressure and possibly in the development of glaucoma.

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INTRODUCTION

Glaucoma is the leading cause of irreversible blindness affecting more than 60 million people worldwide.[1] The risk and prognosis of primary open-angle glaucoma (POAG), the most common type of glaucoma, is influenced by demographic factors such as age, race and family history, and by several ocular parameters including myopic refractive error, optic disc shape and corneal thickness.[2–4] Increased intraocular pressure (IOP) is the most important modifiable risk factor for POAG,[5,6] but there is substantial interest in identifying other potentially modifiable risk factors.

Systemic hypertension may contribute to increased IOP via overproduction or impaired outflow of aqueous humor.[7,8] Some,[9–14] but not all[15–19] population studies have found statistically significant positive associations between systolic blood pressure (SBP) and diastolic blood pressure (DBP) with IOP. Furthermore, the literature on the association between blood pressure (BP) and POAG is limited and inconsistent.[20–23] Qualitative reviews have summarized the evidence on BP, IOP and glaucoma,[7,24,25] but these reviews did not conduct systematic searches of the literature to incorporate all relevant studies and did not produce quantitative estimates of the associations. In addition, most studies included in these reviews were published before 2005. The objective of this meta-analysis was thus to summarize and quantitatively synthesize available literature on the association of BP with IOP and POAG.

MATERIALS AND METHODS

Search Strategy

Our systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[26] To identify relevant studies,

we searched MEDLINE and EMBASE for observational studies investigating the relation of BP or hypertension with POAG, IOP or ocular hypertension (OHT) with no restrictions on language or publication date. The search period was through April 2013. Key words included systolic blood pressure, diastolic blood pressure, blood pressure, hypertension, intraocular pressure, intraocular tension, eye pressure, eyeball pressure, eye internal pressure, intraorbital pressure, ocular pressure, ocular tension, intraocular hypertension, intraocular tension, and glaucoma. In addition, we manually reviewed the reference lists from relevant original research.

Study Selection

We aimed to identify all relevant observational studies that assessed the association of BP or hypertension with IOP, OHT or POAG in general population settings. We applied the following exclusion criteria: (1) reviews, editorials, or letters; (2) case reports or case series; (3) studies not conducted in humans; (4) studies not conducted in adults; (5) studies conducted in population samples comprised only of patients with established glaucoma or ocular hypertension at baseline; (6) studies not reporting glaucoma, IOP or OHT outcomes; (7) studies not using BP or hypertension as exposure; (8) studies investigating mainly drug effects or metabolism; (9) and studies of populations with specific conditions (e.g., pregnancy or eye surgery) that limit their generalizability to general population samples. Furthermore, since age is a strong risk factor for glaucoma and for hypertension development, we further excluded studies that did not adjust for age in the design or the analysis.

For studies that did not report POAG separately from other types of glaucoma, we used results for open angle glaucoma or glaucoma as endpoints. For studies that reported both cross-sectional associations at baseline and prospective longitudinal associations, we included both associations separately by design. If more than one paper reported on the same association

within a study population, we selected the publication with the largest sample size or the longest follow-up. Several studies reported estimates of measures of association without standard errors or any other estimates of statistical variability. These studies were included in the systematic review, but were excluded from the quantitative meta-analysis.

Data Extraction and Quality Assessment

Two investigators (D.Z and M.K.) independently reviewed all search results to identify eligible papers and abstracted data from selected articles, including study design, study population, age and sex distribution, sample size, study outcomes, duration of follow-up, exposure and outcome assessment, main results, and variables included in the adjusted model. Discrepancies between reviewers were solved by consensus. We assessed the risk of bias in studies using the methods described by Sanderson et al[27] and Viswanathan et al.[28] We examined the methods for selecting study participants, the criteria for defining exposures and outcomes, the risk of bias associated with different designs, the methods used to control for confounding, and potential conflicts of interest.

Statistical Analysis

The study endpoints were POAG, IOP, and OHT. We used as many endpoints as reported in each study and conducted separate meta-analyses for each end point (**Table 1**). For hypertension, we combined hazard ratios, odds ratios, and relative risks for POAG or OHT comparing participants with vs. those without hypertension, and average differences in IOP (in mmHg) comparing participants with vs. those without hypertension. For SBP and DBP, we combined hazard ratios, odds ratios or relative risks for POAG or OHT associated with an increase in 10 mmHg for SBP and in 5 mmHg for DBP, and average differences in IOP (in

mmHg) associated with an increase in 10 mmHg for SBP and in 5 mmHg for DBP. These measures of association and their 95% confidence intervals (CIs) were abstracted or derived from published data. For studies reporting standardized regression coefficients, we used the standard deviations for BP and IOP reported for that population to recalculate unstandardized regression coefficients. Finally, for studies reporting measures of association based on log-transformed SBP or DBP, we calculated the measures of association based on 10 and 5 mmHg increases in SBP or DBP, respectively, calculated from the population mean.

When several models for a given endpoint were reported in the same study, we selected the maximally adjusted model. For studies reporting results separately by subgroups (e.g., men and women, hypertension with and without medication, hypertension only and with other diseases, or participants from different locations), we used each group as an independent result for the meta-analyses. For studies reporting both overall and subgroup results, we used overall estimates.

We used DerSimonian and Laird's random-effects models to calculate summary relative risks across studies. Between-study heterogeneity was quantified using the I^2 statistic, which describes the proportion of total variation in study estimates due to heterogeneity. We also assessed the relative influence of each study by omitting one study at a time from the pooled analysis. Publication bias was evaluated using funnel plots and Egger's tests. The funnel plots depict the distribution of the measures of association vs. their standard errors. The null hypothesis of Egger's test is that the regression of measures of association over their standard error has an intercept of zero. The rejection of the null hypothesis ($p < 0.05$) suggests that the measures of association depend on the study sample size, which may reflect publication bias.[29] We assessed heterogeneity of the association of hypertension or BP with study outcomes by

study type (case-control, cross-sectional, longitudinal), location (Europe, America, Asia, others), and year of publication (<2000, ≥2000) using meta-regression with restricted maximum likelihood estimates of between-study variance. We did additional meta-regression by adjustment for IOP (Yes, No) and adjustment for central corneal thickness (Yes, No).

Studies presenting measures of association for BP in 3 or more categories or as continuous exposures were also combined using a random-effects dose-response meta-analysis as described by Greenland and Longnecker.[30,31] One study reporting the dose-response association between BP and POAG was excluded because of the small number of POAG cases in each BP interval.[32] All statistical analyses were conducted with Stata version 12 (STATA Corp, College Station, TX).

RESULTS

Study Characteristics

We identified 60 studies (44 cross-sectional, 9 case-control, and 7 longitudinal cohort studies) that met our inclusion criteria (**Figure 1, Supplemental Table 1**). Twenty-six studies were performed in Asia, 13 in the US, 9 in Europe, 3 in the West Indies, 3 in Australia, 3 in Canada, 2 in the Middle East, and 1 in Congo. The prevalence of POAG in cross-sectional studies ranged from 0.7% to 9%. The number of studies that presented quantitative estimates and 95% CIs that could be incorporated our meta-analysis was 29 for POAG (27 with estimates for hypertension, 10 for SBP and 8 for DBP), 5 for OHT (4 with estimates for hypertension, 1 for SBP and 1 for DBP), and 18 for IOP (3 for hypertension, 17 for SBP and 14 for DBP).

POAG, open angle glaucoma and glaucoma criteria differed across studies. To identify and define glaucoma cases, 9 studies considered characteristics of the optic disc, anterior

chamber angle, optic nerve damage or visual field changes, 14 studies also considered OHT as an additional criteria, 2 studies used self-reported glaucoma, 1 study used medical history records, and 1 study used ICD-9 codes from a medical database. Among the studies that assessed the association between BP and IOP, five measured IOP using a Goldmann applanation tonometer, while the rest used non-contact tonometers, Schiotz tonometers, or handheld tonometers. The average IOP of the study populations ranged from 11.5 to 16.1 mm Hg (**Table 1**). For studies reporting OHT as an outcome, 1 study defined OHT as IOP > 20 mmHg, 1 as IOP ≥ 21 mmHg, 3 as IOP > 21 mmHg. The studies also differed in their definition and ascertainment methods for hypertension (**Supplemental Table 2**), and in the covariates adjusted for (**Supplemental Table 3**).

Primary open angle glaucoma

The association between hypertension and POAG was heterogeneous across studies. Eighteen studies reported a positive association while 9 studies reported an inverse or null association. Seven studies adjusted for IOP and two studies adjusted for central corneal thickness (CCT) in their analysis. The pooled relative risk (RR) for POAG comparing participants with vs. those without hypertension was 1.16 (95% CI 1.05 – 1.28), with modest across study heterogeneity (I^2 34.5%) (**Figure 2**). The pooled RR was significant for cross-sectional studies (1.24, 95% CI 1.06 – 1.44) but it was smaller and not statistically significant for case-control (1.08, 95% CI 0.92 – 1.28) and longitudinal studies (1.05, 95% CI 0.69 – 1.59), although only two longitudinal studies contributed to the pooled estimates. The overall pooled RR in sensitivity analysis based on studies that defined POAG without using IOP as a diagnostic criterion was 1.14 (1.03 – 1.25, I^2 24.0%). In dose-response meta-analysis of studies that presented data using 3 or more categories of BP or that reported BP as a continuous

exposure, the pooled RR for POAG associated with a 10 mm Hg increase in SBP was 1.01 (95% CI 1.00 – 1.03, I^2 26.1%) and the pooled RR associated with a 5 mm Hg increase in DBP was 1.02 (95% CI 0.99–1.04, I^2 25.9%) (**Figure 3**).

Intraocular pressure

Virtually all studies reported a positive association or correlation between SBP, DBP and IOP (**Figure 4, Supplemental Table 4**). The pooled average increase in IOP associated with a 10 mmHg increase in SBP was 0.26 mmHg (95% CI 0.23 – 0.28, I^2 42.5%), and the average increase associated with a 5 mmHg increase in DBP was 0.17 mmHg (95% CI 0.11 – 0.23, I^2 91.2%), with similar results in cross-sectional compared to longitudinal studies. The pooled average difference in IOP comparing participants with vs. those without hypertension was 0.33 mm Hg (95% CI 0.25 – 0.40, I^2 0%), although this estimate was based only on three studies (**Figure 5**).

Only 4 studies assessed the relation between hypertension and OHT, and 3 of these studies were published before 1990. The pooled RR for OHT comparing participants with and without hypertension was 1.26 (0.79 – 2.02, I^2 82.2%) (**Figure 6**). The association between BP levels and OHT was evaluated only in one nested case-control study[15] in which SBP was higher but DBP was not significantly different in OHT cases compared with controls.

Excluding individual studies did not substantially affect the estimates for most associations. The pooled RR estimates after leaving out one study at a time ranged from 1.14 to 1.18 for POAG comparing participants with vs. those without hypertension; from 1.001 to 1.01 for POAG associated with an increase in 10 mmHg of SBP; from 1.004 to 1.01 for POAG associated with an increase in 5 mmHg of DBP; and from 0.99 to 1.44 for OHT comparing participants with vs. those without hypertension. The average increases in IOP after leaving out

one study at a time ranged from 0.24 to 0.26 mmHg per an increase in 10 mmHg of SBP; from 0.15 to 0.18 mmHg per an increase in 5 mmHg of DBP; and from 0.32 to 0.36 mmHg comparing participants with vs. those without hypertension. Egger's tests for publication bias were statistically significant for SBP ($p < 0.001$), hypertension and IOP ($p = 0.045$). Funnel plots suggested that small studies were reporting stronger associations compared to larger studies, but even large studies reported positive associations. (**Supplemental Figure 1**) All studies adjusted for age, but only one study adjusted for age, IOP and CCT at the same time (Vijaya, 2008). For the association between hypertension and POAG, seven studies adjusted for IOP and two studies adjusted for CCT. The associations between the exposures and outcomes were similar among different types of studies, countries, adjustment for IOP and CCT, and year of publication ($p > 0.05$), except for SBP and IOP, as well as SBP and POAG, where the estimate was lower in longitudinal studies compared with cross-sectional studies.

DISCUSSION

In this comprehensive meta-analysis, hypertension and increased SBP and DBP were consistently associated with increased IOP across published studies. Hypertension was also positively associated with the risk of POAG, although the association was significant in cross-sectional but not in case-control or longitudinal studies. The dose-response relationship between SBP and DBP and the risk of glaucoma was also positive but weak. On the other hand, our findings support a role of increased BP in elevated IOP and possibly in the development of POAG.

Several mechanisms may explain an increase in IOP with higher BP. Increasing BP may result in increased production of aqueous humor by means of elevated capillary pressure in the ciliary body.[33] BP may also reduce aqueous humor outflow through elevated episcleral venous

pressure.[34] Indeed, the sympathetic nervous system and the renin-angiotensin system may be involved in the autoregulation of aqueous humour formation, outflow and BP.[24] Experimental models in animals also support a role of BP in IOP levels. Rapid bleeding resulted in a reduction of rate of aqueous formation in monkeys.[24] Angiotensin II receptor blockers (ARB) and angiotensin-converting-enzyme (ACE) inhibitors, which are used for the treatment of hypertension, lower IOP in animals and humans.[35–37] Increased IOP may also mediate the association between BP and POAG, although direct micro-vascular damage caused by hypertension may impact blood perfusion to the optic nerve and cause ganglion cell injury irrespective of IOP levels.[38]

While the association of hypertension with IOP was consistent across studies, the association of hypertension with POAG showed significant heterogeneity, and the dose-response association of BP with POAG was weak. Indeed, a number of studies have found a higher risk of POAG in participants with low BP, [39,40] and a high prevalence of low BP in normal tension glaucoma.[41,42] It has been hypothesized that both hypertension and hypotension are risk factors for POAG.[43] Low BP may compromise the autoregulation of the ciliary artery circulation, impair blood flow to the optic disc, and induce glaucomatous damage.[41,44] In our meta-analysis, several studies showed a J-shaped association between BP and POAG (**Figure 3**). Unfortunately, many studies conducted their analyses assuming a linear dose-response relationship between BP and POAG, and even for studies not assuming linear dose-response relationships, meta-analyses are limited to identify complex dose-response relationships. A J-shaped relation between BP and POAG could explain both the heterogeneity in the association between hypertension and POAG and the small magnitude of the association between BP and POAG in our meta-analysis. Given this evidence, future studies evaluating the association

between BP with POAG should report detailed dose-response relationships and avoid using methods that assume a linear association.

The positive associations of BP and hypertension with IOP were robust across studies conducted in many different settings and with adjustment for a variety of confounders. We attempted to limit the influence of uncontrolled confounders on this meta-analysis by excluding studies that did not adjust for age. Furthermore, the magnitude and direction of the associations did not differ with different degrees of adjustment, suggesting that the results of this meta-analysis were robust to misspecification of known confounders in the analysis. Furthermore, a number of clinical trials and hospital-based studies have supported that antihypertensive medications including calcium-channel blockers, diuretics, ACE inhibitors and β-blockers, administrated either topically or orally, can reduce IOP and slow progression to glaucoma in humans.[45–47] The clinical evidence from the effects of antihypertensive medications also support a causal relation between hypertension, IOP, and POAG. However, the observational evidence between hypertension and POAG summarized in this meta-analysis was largely driven by cross-sectional results. Well conducted longitudinal studies are needed to establish the role of blood pressure on the risk of glaucoma.

Aging is an important confounder in the association between BP, IOP and POAG. Since BP and age are highly correlated, careful interpretation of the association between BP, IOP and POAG should be considered in the context of effect of age. In this meta-analysis, we excluded studies that did not adjust for age, considering that aging would be a crucial confounder for the association between BP, IOP and POAG. However, it was not possible to account for the effects of other age-related risk factors in the current analysis, such as damages of the glial functions due to long and persistent environmental and systematic exposures related with aging.

We found that both high and low BP were associated with increased risk of POAG. While we hypothesized that the increase in BP would be associated with an elevated IOP, leading to increased risk of glaucoma, excessive BP lowering in glaucoma patients may cause a drop in ocular perfusion pressure (arterial BP minus IOP) and ischemic injury, which was also found to be a significant risk factor for glaucoma in large epidemiological studies.[48] Randomized clinical trials also suggested that a low level of BP was associated with risk and progression of glaucoma. In the Early Manifest Glaucoma Trial, lower systolic BP in patients with lower baseline IOP was associated with faster progression for open-angle glaucoma.[49] However, this J-shape association between systolic and diastolic BP with IOP may by confounded by antihypertensive treatment status, as treated or over-treated hypertensive patients can have a normal or low BP but they may have elevated POAG risk. In the Thessaloniki Eye Study, low diastolic ocular perfusion pressure was associated with increased risk for POAG in subjects using antihypertensive treatment.[50] However, in our study, information on antihypertensive treatment was not available in the original studies, and we could not evaluate if the J-shape association was related to use of anti-hypertensive treatment.

Some limitations of our meta-analysis need to be considered. First, studies differed widely in the characteristics of the study populations, the measurement techniques and the definitions of BP, IOP, and glaucoma, and the prevalence of pre-existing comorbidities. The gold standard for measuring IOP is the Goldmann applanantion tonometer.[51] While non-contact tonometers are being widely used in many clinical settings for convenience, there were concerns about their reliabilty in patients with irregular cornea or poor visual acuity, and they could result in more conservative IOP measurements in patients with extreme IOP.[52] Our

sensitivity analysis, however, showed similar associations when the analyses was restricted to studies using Goldmann applanantion tonometers.

Second, most studies measured BP and IOP at a single point in time. Both BP and IOP are subject to substantial within-person variability,[53] which may result in underestimation of the associations. Third, there was also heterogeneity in the measures of association used and in the covariates adjusted for in each study and we also cannot exclude the possibility that individual study results were affected by uncontrolled residual confounding, such as lifestyle or environmental factors. Finally, although the total number of studies was large, there were few prospective cohort studies, making it difficult to assess temporality, a key consideration in establishing causality.

In spite of methodological heterogeneity across studies, we identified a consistent and robust association between BP and IOP. This association was evident across different populations, study designs and publication periods. We also identified a significant association between hypertension and POAG, although there was significant heterogeneity across study designs. Additional prospective studies are needed to firmly establish the role of blood pressure in glaucoma development. Our analysis supports that hypertensive patients should be screened for elevated IOP and higher risk for POAG, and that hypertension management be included as part of POAG treatment regimes.

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Table 1. Characteristics of the studies included in the meta-analysis of the association between blood pressure and primary open-angle glaucoma.

First author, year	Country	Population	Setting	Sample size	Recruit (follow-up) year	Exposure	Outcome	IOP measure	Mean age/ range (yr)	Mean IOP (mm Hg)	Prevalence of POAG/ OHT (%)
Cross-sectional											
Leske, 1983	US	Framingham Heart Study and Framingham Eye Study	Community	2433	1975	HTN	OHT	GAT	NA	NA	NA
David, 1987	Israel	Participants from urban areas in southern Israel	Health screening exam	2594	1984	HTN	OHT	GAT	40-79	15.0	NA
Wormald, 1994	UK	African Caribbean immigrants living in London	Community	873	1991	HTN	Glaucoma	NA	>35	NA	3.5
Dielemans, 1995	Netherlands	The Rotterdam Study	Community	4187	1993	SBP, DBP	IOP	GAT	55-95	14.6	NA
Tielsch, 1995	US	The Baltimore Eye Survey	Community	5308	1988	SBP, DBP, HTN	POAG	NA	>40	NA	3%
Nomura, 1999	Japan	Office workers and their family members	Health screening exam	68998	1997	SBP, DBP	IOP	NCT	20-79	11.8	NA
Bonomi, 2000	Italy	The Egna-Neumarkt Study	Community	4297	NA	HTN	POAG	NA	40-89	NA	1.4
Quigley, 2001	US	Hispanics in Arizona	Community	4774	1990	SBP, DBP, HTN	OAG	GAT	>40	15.6	2
Nomura, 2002	Japan	National Institute for Longevity Sciences–the Longitudinal Study of Aging program (NILS-LSA)	Community	1317	1999	SBP, DBP	IOP	NCT	40-80	13.5	NA
Yoshida, 2003	Japan	Participants from a general hospital	Health screening exam	569	2000	SBP, DBP	IOP	NCT	29–79	12.9	NA
Mitchell, 2004	Australia	The Blue Mountains Eye Study	Community	3654	1994	HTN	OAG	GAT	66.2	NA	3
Bai, 2005	China	Participants in rural province in China	Community	1775	2003	HTN	POAG	PAT	50 - 91	NA	NA
Chen, 2005	Taiwan	Hospital based healthy subjects	Health screening exam	1271	2001	SBP, DBP	IOP	NCT	50.0	13.6	NA
Mitchell, 2005	Australia	The Blue mountains eye study	Community	3302	1994	SBP, DBP	IOP	PAT	49-97	NA	NA
Oh, 2005	South Korea	Healthy visitors to health promotion center	Health screening exam	943	2003	SBP	IOP	NCT	45.8	15.4	NA
Hulsman, 2007	Netherlands	The Rotterdam Study	Community	5317	1993	SBP, DBP	OAG	GAT	68.8	16.0	4

Vijaya, 2008	India	The Chennai Glaucoma Study	Community	3850	2004	HTN	POAG	GAT	54.8	15.2	3.5
Tan, 2009	Singapore	The Singapore Malay Eye Study	Community	3280	2006	SBP, DBP, HTN	POAG	GAT	58.7	NA	3.2
Wang, 2009	China	The Beijing Eye Study	Community	3222	2006	HTN	POAG	NCT	60.4	15.7	2.4
Chang, 2010	Taiwan	University Hospital	Health screening exam	1044	2006	SBP, DBP	IOP	NCT	50.8	14.5	NA
Imai, 2010	Japan	General hospital	Health screening exam	14003	2008	HTN	OHT	NCT	18-83	14.8	NA
Memarzadeh, 2010	US	Los Angeles Latino Eye Study	Community	6130	2003	SBP, DBP	OAG	GAT	54.7	14.2	4.7
Park, 2010	South Korea	Kyunggi Province	Community	446	2008	SBP, DBP	IOP	NCT	41.6	12.4	NA
Graw, 2011	Germany	KORA Eye Study	Community	2593	1999	HTN	Glaucoma	NA	32-71	NA	1.5
Ishikawa, 2011	Japan	Subjects attending community health screenings	Health screening exam	710	2007	HTN	POAG	GAT	>30	15.1	3.7
Topouzis, 2011	Greece	Thessaloniki Eye Study	Community	2261	1999	HTN	POAG	GAT	70.4	15.9	6
Goldacre, 2012	UK	Analysis of the Oxford Record Linkage Study (ORLS) and English Linked Hospital Episode Statistics (LHES)	Community	94591	ORLS: 1963-1998 LHES: 1999-2010	HTN	Glaucoma	NA	0-80+	NA	1.1
Kim, 2012	South Korea	Survey of local residents	Community	1464	2006	HTN	POAG	GAT	63.7	13.5	3.8
Lee, 2012	South Korea	Healthy Twin Study	Community	3096	2005	SBP	IOP	NCT	37.8	13.7	NA
Sun, 2012	China	Villagers	Community	4956	NA	HTN	POAG	PAT	>40	14.0	0.7
Case-control											
Morgan, 1975	Canada	Cases drawn from University of British Columbia, and from a private practitioner with a large glaucoma referral practice	Hospital outpatient clinic	91 cases, 91 controls	NA	HTN	POAG, OHT	NA	NA	NA	NA
Reynolds, 1977	US	Records from pathology clinic	Hospital outpatient clinic	87 cases, 87 controls	1975	HTN	OAG	NA	≥18	NA	NA
Wilson, 1987	US	Patients from General Eye Service(GES) of the Massachusetts Eye and Ear Infirmary (MEEI)	Community	121 cases, 237 controls	1984	SBP, HTN	POAG	NA	NA	NA	NA
Katz, 1988	US	Patients from Wilmer Institute, Johns Hopkins Hospital	Hospital outpatient clinic	94 cases, 94 controls	NA	SBP, DBP, HTN	Glaucoma	GAT	NA	NA	NA

Uhm, 1992	US	Patients from Kresge Eye Institute	Hospital outpatient clinic	361 cases, 927 controls	NA	HTN	POAG	GAT	65.5	NA	NA
Charliat, 1994	US	Patients from private practice and public hospitals	Hospital outpatient clinic	175 cases,175 controls	1994	HTN	POAG	GAT	65.7	16.9	NA
kaimbo, 2001	Congo	Patients from an ophthalmologic clinic	Hospital outpatient clinic	40 cases, 104 controls	1997	SBP, DBP, HTN	OAG	GAT	28-81	19.3	NA
Fan, 2004	China	Patients from a hospital	Hospital outpatient clinic	32 cases,96 controls	2000	HTN	POAG	GAT	32-71	20.6	NA
Orzalesi, 2007	Italy	Patients from outpatient clinic	Hospital outpatient clinic	2,879 cases, 973 controls	NA	HTN	POAG	GAT	67.2	16.2	NA
Longitudinal											
Mcleod, 1990	US	Baltimore Longitudinal Study of Aging	Community	572	1966, 6 yr follow-up	SBP, DBP	IOP	ST	19-89	16.1	NA
Hennis, 2003	West Indies	Barbados eye study	Community	2996	1988, 4 yr follow-up	HTN	IOP	GAT	57.5	18.4	NA
Klein, 2005	US	Beaver Dam study	Community	4926	1990, 5 yr follow-up	SBP, DBP	IOP	GAT	60.4	15.4	NA
Nakano, 2005	Japan	Male aircraft crew members	Community	2330	1985, 5 year follow-up	SBP, DBP	IOP	GAT	35.9	13.8	NA
Wu, 2006	West Indies	Barbados Eye Study	Community	2298	1992, 9 yr follow-up	SBP, DBP	IOP	GAT	55.1	17.5	NA
Leske, 2008	West Indies	Barbados Eye Study	Community	3222	1992, 9 yr follow-up	SBP, DBP, HTN	OAG	NA	56.9	18.0	NA
Newman-Casey, 2011	US	InVision Data Mart database	Community	2182315	2001, 6 yr follow-up	HTN	OAG	NA	54.5	NA	Incidence: 2.5

*HANES: Health and Nutrition Exam Survey; GAT: Goldmann Applanation Tonometer; ST: Schiotz tonometer; PAT: Perkins applanation tonometer; NCT: Non-contact tonometer; IOP: Intraocular pressure; POAG: Primary open-angle glaucoma; OAG: Open-angle glaucoma; OHT: Ocular hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HTN: Hypertension; NA: Not available.

Figure 1. Flow chart of study selection process for the meta-analysis of the association between blood pressure and primary open-angle glaucoma.

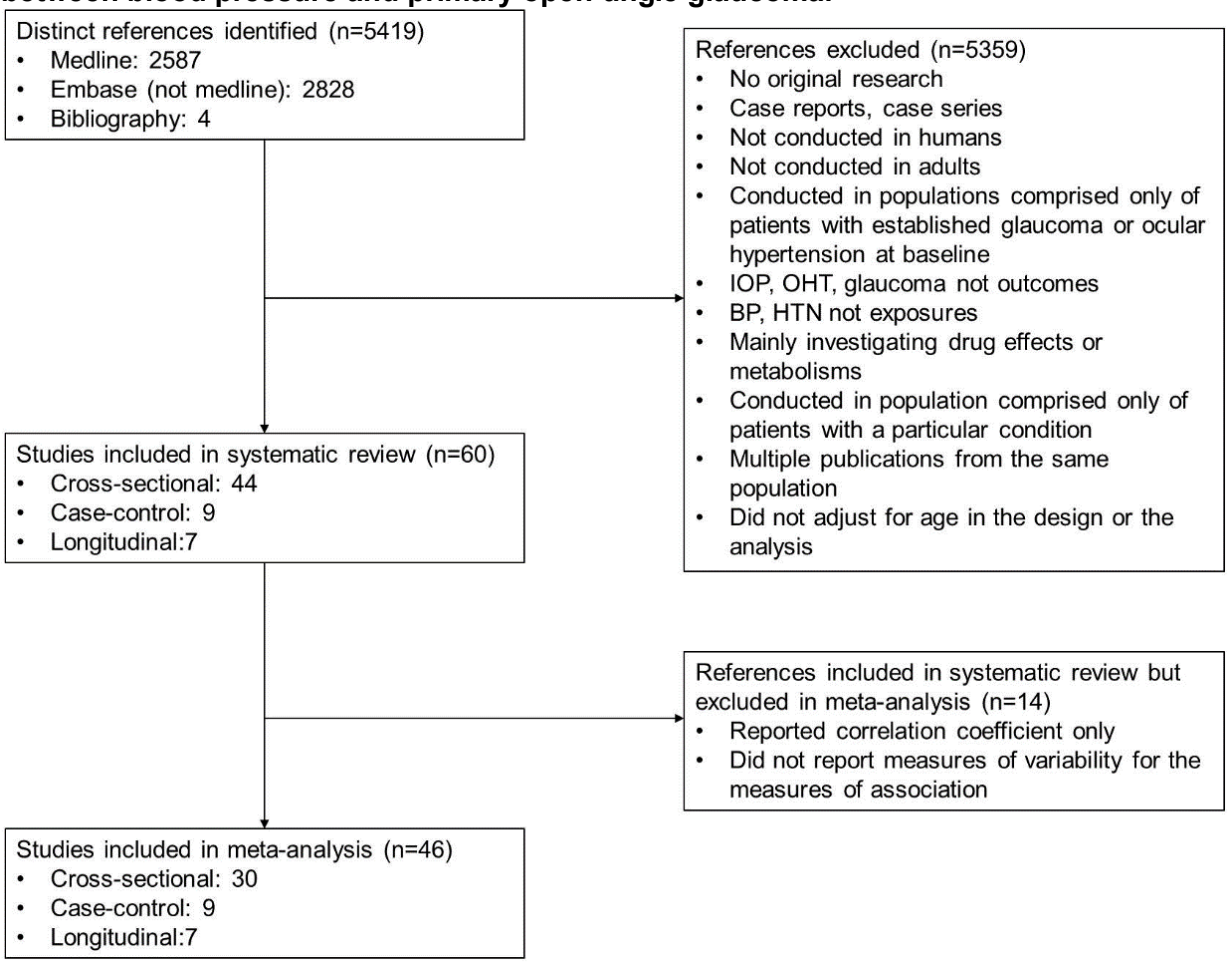
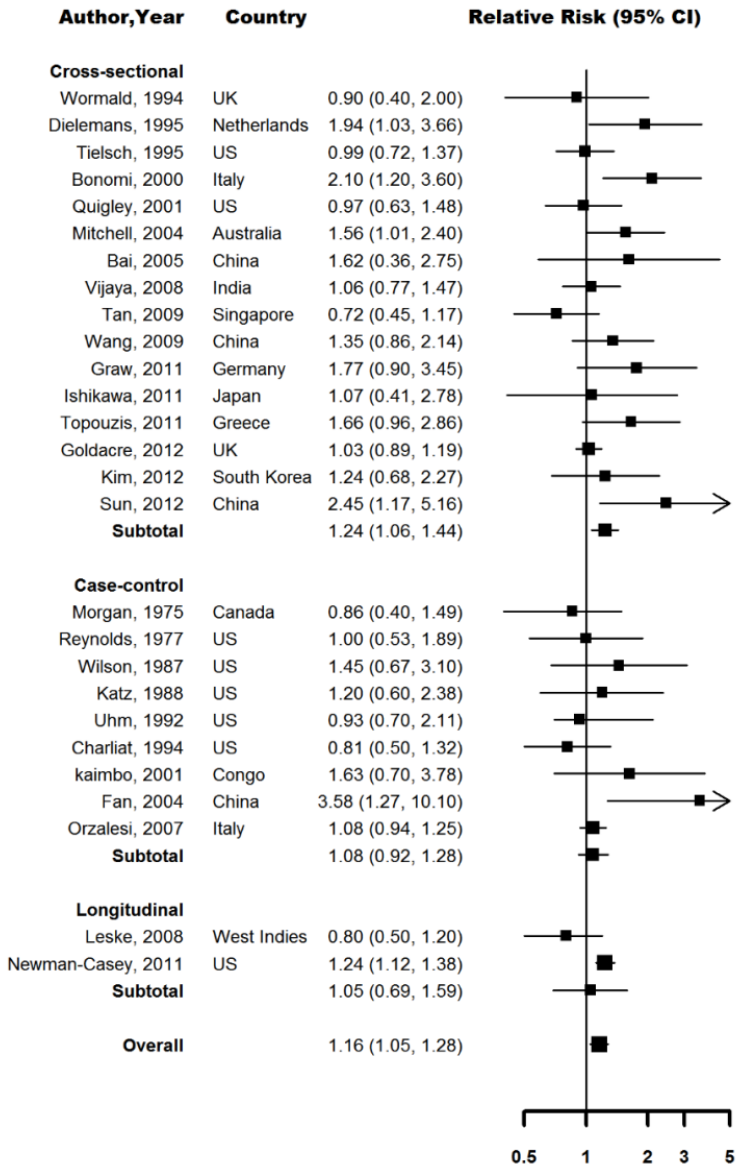
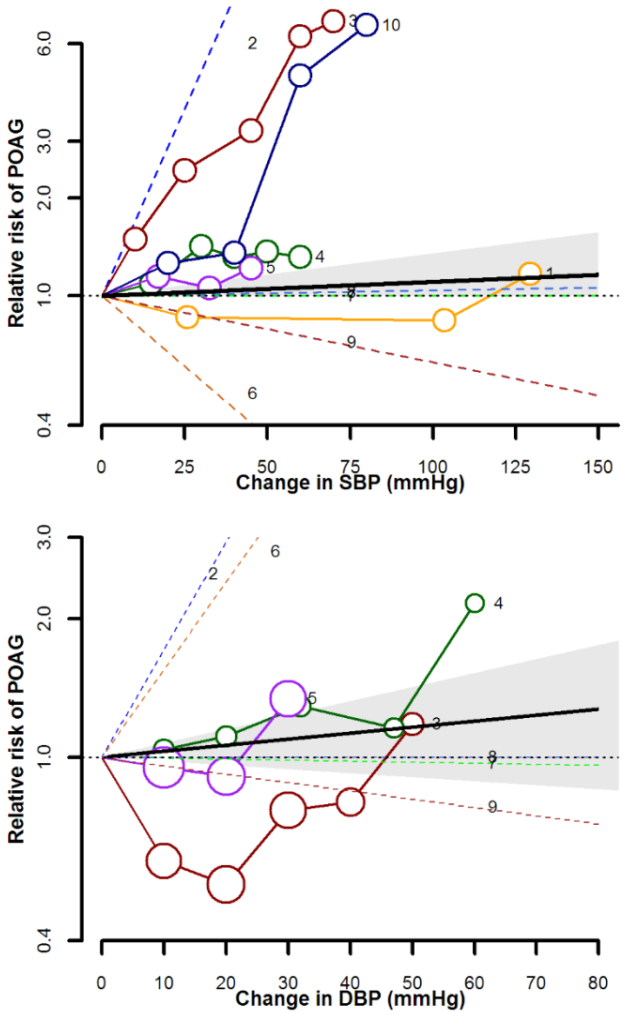


Figure 2. Relative risks for primary open-angle glaucoma comparing patients with to those without hypertension.



The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate. Horizontal lines represent 95% confidence intervals.

Figure 3. Relative risk for primary open-angle glaucoma with increasing levels of blood pressures in dose-response meta-analysis.



Circle areas are inversely proportional to the variance of the log relative risks from studies using categorical systolic blood pressure or diastolic blood pressure intervals. Dashed lines correspond to studies that used systolic blood pressure or diastolic blood pressure as a continuous variable. The pooled linear risk trend (thick solid line) and its 95% confidence band (shaded region) were obtained using a random-effects dose-response meta-analysis. The individual studies were: 1: Tan et al., 2009; 2: Kaimbo et al., 2001; 3: Memarzadeh et al., 2010; 4: Tielsch et al., 1995; 5: Hulsman et al., 2007; 6: Katz et al., 1988; 7: Quigley et al., 2001; 8: Dielemans et al., 1995; 9: Leske et al., 2008; 10: Wilson et al., 1987.

Figure 4. Increase in intraocular pressure associated with a 10 mm Hg increase in systolic blood pressure and a 5 mm Hg increase in diastolic blood pressure.

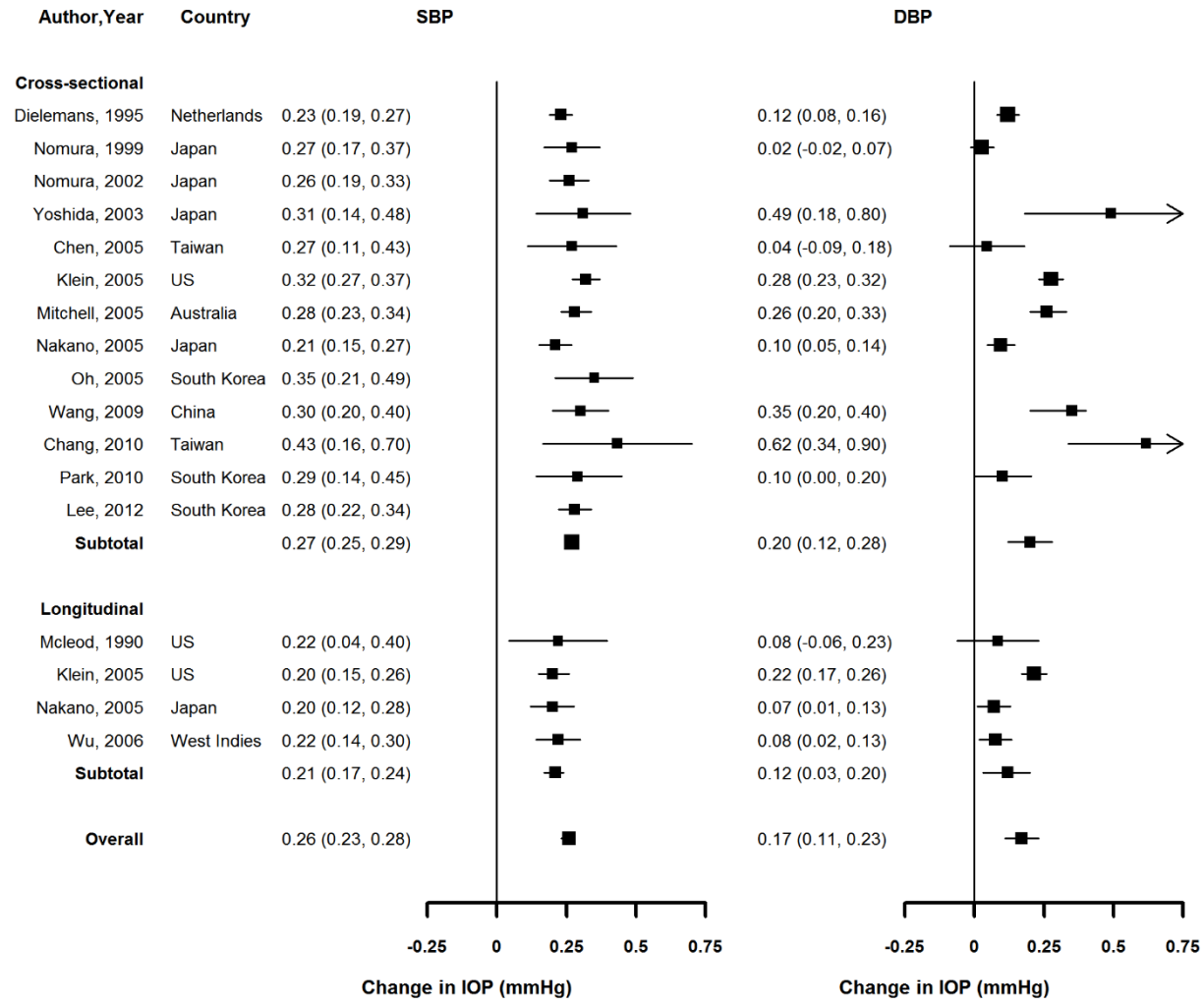


Figure 5. Increase in intraocular pressure comparing patients with to those without hypertension.

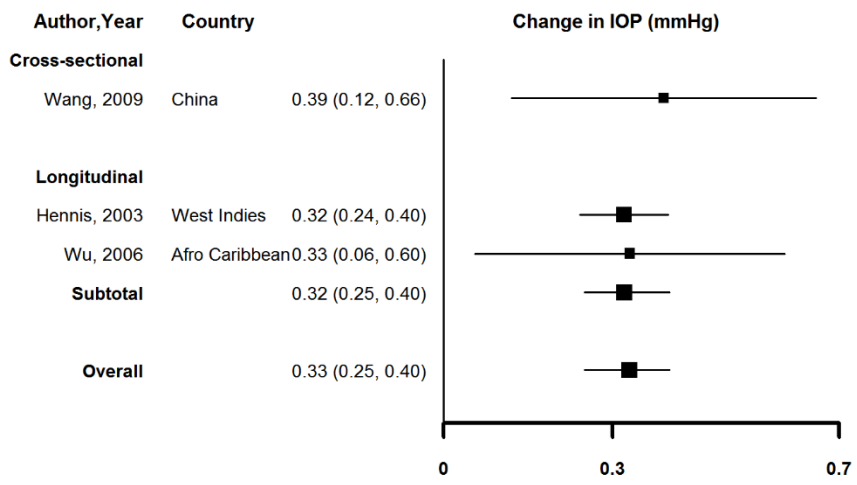
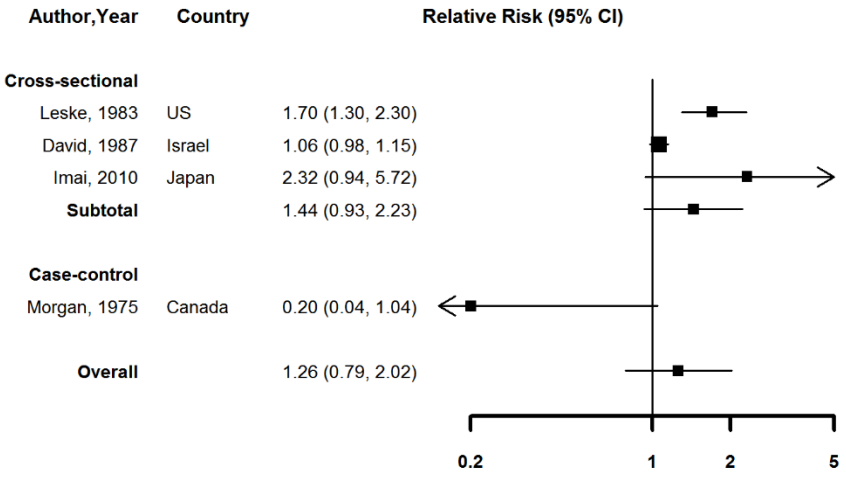


Figure 6. Relative risk for ocular hypertension comparing participants with to those without hypertension.



Supplemental Table 1. References of studies included in the meta-analysis of the association between blood pressure and primary open-angle glaucoma.

Cross-sectional

1 Leske MC, Podgor MJ. Intraocular pressure, cardiovascular risk variables, and visual field defects. Am J Epidemiol. 1983;118(2):280-287.

2 David R, Zangwill L, Stone D, Yassur Y. Epidemiology of intraocular pressure in a population screened for glaucoma. Br J Ophthalmol. 1987;71(10):766-771.

3 Wormald RP, Basauri E, Wright LA, Evans JR. The African Caribbean Eye Survey: risk factors for glaucoma in a sample of African Caribbean people living in London. Eye Lond Engl. 1994;8 (Pt 3):315-320.

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5 Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol. 1995;113(2):216-221.

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24 Graw J, Welzl G, Ahmad N, et al. The KORA Eye Study: a population-based study on eye diseases in Southern Germany (KORA F4). Invest Ophthalmol Vis Sci. 2011;52(10):7778-7786.
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26 Topouzis F, Wilson MR, Harris A, et al. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. Am J Ophthalmol. 2011;152(2):219-228.e1.
27 Goldacre MJ, Wotton CJ, Keenan TDL. Risk of selected eye diseases in people admitted to hospital for hypertension or diabetes mellitus: record linkage studies. Br J Ophthalmol. 2012;96(6):872-876.
28 Kim M, Kim T-W, Park KH, Kim JM. Risk factors for primary open-angle glaucoma in South Korea: the Namil study. Jpn J Ophthalmol. 2012;56(4):324-329.
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30 Sun J, Zhou X, Kang Y, et al. Prevalence and risk factors for primary open-angle glaucoma in a rural northeast China population: a population-based survey in Bin County, Harbin. Eye Lond Engl. 2012;26(2):283-291.

Case-control

1 Morgan RW, Drance SM. Chronic open-angle glaucoma and ocular hypertension. An epidemiological study. Br J Ophthalmol. 1975;59(4):211-215.
2 Reynolds DC. Relative risk factors in chronic open-angle glaucoma: an epidemiological study. Am J Optom Physiol Opt. 1977;54(2):116-120.
3 Wilson MR, Hertzmark E, Walker AM, Childs-Shaw K, Epstein DL. A case-control study of risk factors in open angle glaucoma. Arch Ophthalmol. 1987;105(8):1066-1071.
4 Katz J, Sommer A. Risk factors for primary open angle glaucoma. Am J Prev Med. 1988;4(2):110-114.
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7 Kaimbo DK, Buntinx F, Missotten L. Risk factors for open-angle glaucoma: a case-control study. J Clin Epidemiol. 2001;54(2):166-171.
8 Fan B, Leung Y, Wang N, et al. Genetic and environmental risk factors for primary open-angle glaucoma. Chin Med J (Engl). 2004;117(5):706-710.
9 Orzalesi N, Rossetti L, Omboni S. Vascular risk factors in glaucoma: the results of a national survey. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Für Klin Exp Ophthalmol. 2007;245(6):795-802.

Longitudinal

1 McLeod SD, West SK, Quigley HA, Fozard JL. A longitudinal study of the relationship between intraocular and blood pressures. Invest Ophthalmol Vis Sci.

1990;31(11):2361-2366.
2 Hennis A, Wu S-Y, Nemesure B, Leske MC. Hypertension, diabetes, and longitudinal changes in intraocular pressure. Ophthalmology. 2003;110(5):908-914.
3 Klein BEK, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. Br J Ophthalmol. 2005;89(3):284-287.
4 Nakano T, Tatemichi M, Miura Y, Sugita M, Kitahara K. Long-term physiologic changes of intraocular pressure: a 10-year longitudinal analysis in young and middle-aged Japanese men. Ophthalmology. 2005;112(4):609-616.
5 Wu S-Y, Nemesure B, Hennis A, Leske MC. Nine-year changes in intraocular pressure: the Barbados Eye Studies. Arch Ophthalmol. 2006;124(11):1631-1636.
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7 Newman-Casey PA, Talwar N, Nan B, Musch DC, Stein JD. The relationship between components of metabolic syndrome and open-angle glaucoma. Ophthalmology. 2011;118(7):1318-1326.

Supplemental Table 2. Hypertension ascertainment method in studies included in meta-analysis of the association between blood pressure and primary open-angle glaucoma.

First author, year	SBP, mm Hg	DBP, mm Hg	Medication	Self-report history	Medical record
Morgan, 1975	-	-	Y	-	-
Reynolds, 1977	Age<44:>140 Age 45-64:>150 Age≥65: >160	Age<44:>90 Age 45-64:>95 Age≥65: >95	-	-	-
Wilson, 1987	≥160	-	Y	-	-
Katz, 1988	-	-	Y	-	-
Uhm, 1992	-	-	-	Y	-
Charliat, 1994	-	-	-	Y	-
Dielemans, 1995	≥160	≥95	-	-	-
Tielsch, 1995	≥140	≥90	Y	-	-
Bonomi, 2000	>160	>95	Y	-	-
kaimbo, 2001	≥160	≥95	Y	Y	-
Quigley, 2001	≥160	≥90	Y	-	-
Fan, 2004	-	-	-	Y	-
Mitchell, 2004	≥160	≥95	Y	Y	-
Bai, 2005	>160	>95	-	Y	-
Orzalesi, 2007	-	-	-	Y	-
Leske, 2008	≥140	≥90	Y	-	-
Vijaya, 2008	≥140	≥90	Y	-	-
Tan, 2009	≥130	≥85	Y	-	-
Wang, 2009	≥140	≥90	Y	-	-
Graw, 2011	≥140	≥90	Y	Y	-
Ishikawa, 2011	≥140	≥90	-	-	-
Newman-Casey, 2011	-	-	-	-	Y
Topouzis, 2011	≥140	≥90	-	-	-
Goldacre, 2012	-	-	-	-	Y
Kim, 2012	-	-	-	Y	-
Sun, 2012	≥140	≥90	Y	-	-

*-: not used in ascertaining hypertension; Y: used in ascertaining hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Supplemental Table 3. Covariates adjusted in studies included in meta-analysis of the association between blood pressure and primary open-angle glaucoma.

First author, year	Covariates
Cross-sectional	
Leske, 1983	Age, sex
David, 1987	Age
Wormald, 1994	Age, sex, diabetes, skin color, place of birth
Dielemans, 1995	Age, sex, BMI
Tielsch, 1995	Age, race
Nomura, 1999	Age, BMI, DBP, SBP
Bonomi, 2000	Age, sex
Quigley, 2001	Age
Nomura, 2002	Age, CCT, BMI, sex
Yoshida, 2003	Age, BMI, SBP, alcohol, smoking, exercise , coffee
Mitchell, 2004	Age, sex, maximum IOP, glaucoma family history, myopia, current thyroxine use, pseudoexfoliation, and diabetes
Bai, 2005	Age, sex
Chen, 2005	Age, glucose, triglyceride, sex
Mitchell, 2005	Age, diabetes, smoking, myopia, iris color, glaucoma family history, pseudoexfoliation
Oh, 2005	Age, sex, weight, height, BMI, waist circumference, body fat percent, blood pressure, LDL cholesterol, HDL cholesterol, log triglycerides, log fasting insulin, and/or the insulin sensitivity indices
Hulsman, 2007	Age, sex, BMI, smoking, diabetes mellitus, serum cholesterol level, and BP-lowering treatment
Vijaya, 2008	Age, sex, IOP, CCT, myopia
Tan, 2009	Age, sex, education, smoking status, central corneal thickness, and diabetic treatment (none, diet, or oral/insulin)
Wang, 2009	Age, sex, area of habitation, BMI, glucose, cholesterol, LDL, HDL, education, income
Chang, 2010	Age, sex
Imai, 2010	Age, maximum temperature, abdominal circumference, fasting glucose, HDL, triglyceride
Memarzadeh, 2010	Age, IOP, history of glaucoma treatment, history of elevated BP and treatment of BP
Park, 2010	Age, waist, triglyceride
Graw, 2011	Age, sex
Ishikawa, 2011	Age, sex, diastolic blood pressure, intraocular pressure, ocular perfusion pressure
Topouzis, 2011	Age, IOP, diabetes, diabetes treatment, coronary artery bypass or vascular surgery, myopia
Goldacre, 2012	ORLS: Age, sex, time-period, district of residence in the ORLS datasets LHES: Age, sex, time-period, region of residence and deprivation score associated with patients' area of residence
Kim, 2012	Age, diabetes, thyroid disease, family history of glaucoma, IOP
Lee, 2012	Age, sex
Sun, 2012	Age, family history of glaucoma, IOP
Case-control	
Morgan, 1975	Age, sex, education, income
Reynolds,	Age, sex and race

1977	
Wilson, 1987	Age, sex, race, family history of POAG, SBP, smoking, myopia, radiation exposure, metal exposure, and reason for attendance at our general eye service
Katz, 1988	Age, race and sex
Uhm, 1992	Age, race, diabetes, family history of glaucoma
Charliat, 1994	Age at time of diagnosis (±2 years), type of health care (public hospital vs. private practice), sex
kaimbo, 2001	Age, gender, Mongo, Born place, Diet habbit (rice vs others), family history of glaucoma, diabetes, alcohol, smoking, hyperopia, cataract, BMI
Fan, 2004	Age, sex, family history of glaucoma, cigarette smoking, alcohol consumption, myocilin sequence alteration T353i
Orzalesi, 2007	Age
Longitudinal	
Mcleod, 1990	Baseline age, baseline IOP, baseline BP
Hennis, 2003	Age, baseline IOP, diabetes history,
Klein, 2005	Age, sex, baseline IOP, BP medication, diabetes
Nakano, 2005	Age and gender
Wu, 2006	Age, sex, and baseline IOP
Leske, 2008	Age, gender, IOP, and IOP- and blood pressure–lowering treatment
Newman-Casey, 2011	Age, sex, race, education level, house-hold net worth, region of residence at the time of medical plan enrollment, cataract, pseudophakia or aphakia, macular degeneration, diabetic retinopathy, hypotension, sleep apnea syndrome, migraine headache, Charlson comorbidity index, and each of the other metabolic syndrome

*BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CCT: Central corneal thickness; IOP: Intraocular pressure; LDL: Low density lipoprotein; HDL: High density lipoprotein; POAG: Primary open-angle glaucoma; BP: Blood pressure; ORLS: Oxford Record Linkage Study; LHES: English linked hospital episode statistics

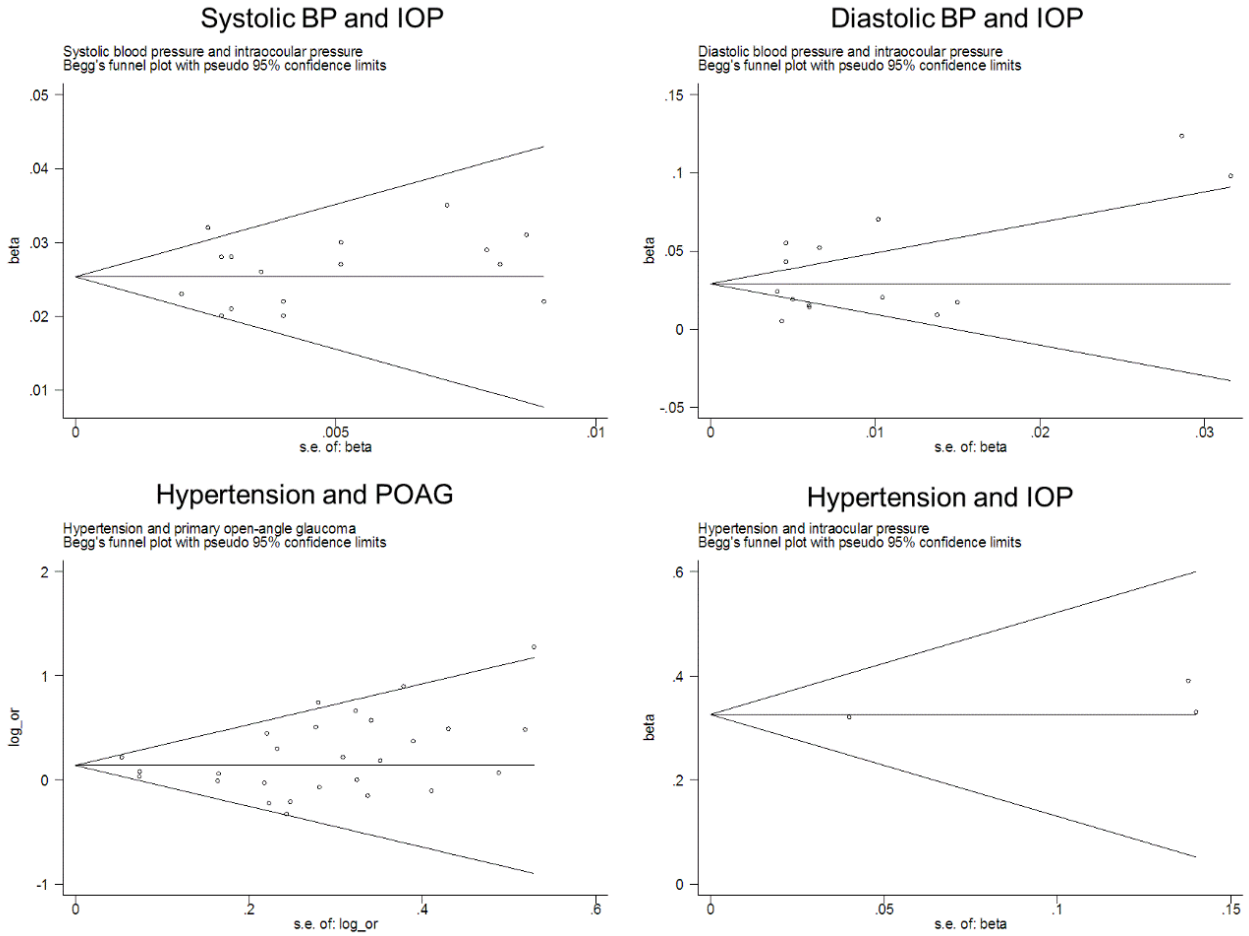
Supplemental Table 4. Studies of intraocular pressure included in systematic review but not included in the meta-analysis (all are cross-sectional)

First author, year	Country	Population	Setting	Measurement	Exposure	Recruit year	sample size	Mean IOP (mm Hg)	Mean age	Correlation coefficient	Regression coefficient	Covariates
Bulpitt, 1975	UK	Survey of patients in London	Community	PAT	SBP	1971	555	3-36	age>60		0.023 (p<0.001)	Sex, age, DBP, Hb, height, weight, ponderal index
Shiose, 1984	Japan	Office workers	Health screening exam	ST/NCT	SBP, DBP	1981	192138	Male: 14.8 Female :15.3	-		SBP: 0.02 DBP: 0.02	Age
Shulzer, 1987	Canada	NA	NA	NCT	SBP	NA	232	Normal: 15. 4 OHT: 26.2	Normal: 63.6 OHT: 59.8	-0.172 (p=0.13)		Age
Krieger, 1988	US	American indians with diabetes and obesity	Community	GAT	mean BP	NA	560	NA	12- 89		0.135 (p=0.02)	Ideal weight index
Qureshi, 1997	Pakistan	White and blue colar workers	Community	GAT	SBP, DBP	NA	3317	NA	21-60		SBP: 0.03 (p<0.05) DBP: 0.01 (P>0.05)	Age, heart rate, weight
Rochtchina Mapplstat, 2002	Australia	Population-based survey	Community	GAT	SBP	1994	3654	16	≥49		0.213 (p<0.001)	Age, family history of glaucoma, diabetes, myopia
Lin, 2005	Taiwan	Randomly sampled	Community	NCT	SBP	2000	1292	12.9	≥65		0.194 (p<0.001)	Age, diabetes, sex, alcohol
Kawase, 2008	Japan	Taijimi study	Community	NCT	Mean BP	2000	2597	Left: 14.5 Right: 14.5	57.0		0.121 (p<0.0001)	Age, BMI, SBP, DBP, a history of diabetes, a history of smoking, CCT, radius of corneal curvature, refractive error
Lee, 2008	South Korea	Visitors of Health Promotion Medical	Health screeni	NCT	SBP	2001	16383	Male: 12.3	Male: 46.5		Male: 0.151 (p<0.001)	Age, triglyceride, HDL, LDL, smoking, total

		Center	ng exam					Female : 11.8	Female : 46.1		Female: 0.189 (p<0.001)	cholesterol
Wong, 2009	Singapore	The Singapore Malay Eye Study	Community	GAT	SBP	2006	3280	NA	40-80		0.033 (p<0.001)	Age, SBP, CCT, sex, spherical equivalent, diabetes, and smoking
Tomoyose, 2010	Japan	The Kumejima Study	Community	GAT	SBP, DBP	2005	2,838	15.1	58.4	SBP: 0.23 (P <.001) DBP: 0.19 (P< .001)	SBP: 0.025 (p<0.001)	Age, gender, BMI, corneal curvature, axial length
Wang, 2011	China	The Liwan Eye Study	Community	NCT	HTN	2004	1348	15.2	65.1		0.82 (p<0.001)	Age, gender, BMI, CCT
Suh, 2012	South Korea	The Namil Study	Community	GAT	HTN	2008	3191	14.1	58.7	0.62	0.408 (p<0.05)	Age, sex, area, CCT, Refractive error, cup to disc ratio, family history of glaucoma, diabetes, CVD, smoking
Hoehn, 2013	Germany	The Gutenberg Heath Study	Community	NCT	HTN	2008	4335	14.0	54.7		Men: 0.370 (p=0.001) Women: 0.488 (p<0.001)	Age, iris color, CCT, diabetes, waist-to-hip ratio, smoking, dyslipidemia

*GAT: Goldmann Applanation Tonometer; ST: Schiotz tonometer; PAT: Perkins applanation tonometer; NCT: Non-contact tonometer; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CCT: Central corneal thickness; IOP: Intraocular pressure; LDL: Low density lipoprotein; HDL: High density lipoprotein; POAG: Primary open-angle glaucoma; BP: Blood pressure

Supplemental Figure 1. Funnel plots for the meta-analyses of systolic and diastolic blood pressure with intraocular pressure and hypertension with intraocular pressure and primary open-angle glaucoma.



CHAPTER 3

DIABETES, FASTING GLUCOSE, AND THE RISK OF GLAUCOMA: A META-ANALYSIS

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ABSTRACT

Topic: We performed a meta-analysis to summarize the association of diabetes and blood glucose levels with glaucoma, intraocular pressure (IOP) and ocular hypertension in the general population.

Clinical relevance: Diabetes has been proposed as a risk factor for glaucoma, but epidemiological studies have been inconsistent and the association is still controversial. Cohort studies have never been appraised systematically. Furthermore, there are no systematic reviews evaluating other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma.

Methods: Studies were identified by searching the PubMed and EMBASE databases. Inverse-variance weighted random-effects models were used to summarize relative risks across studies.

Results: We identified 47 studies including 2,981,342 individuals from 16 countries. The pooled RR for glaucoma comparing patients with to those without diabetes was 1.48 (95% CI 1.29 – 1.71), with significant heterogeneity across studies (I^2 82.3%, $p < 0.001$). The risk of glaucoma increased by 5% (95% CI 1 – 9%) for each year since diabetes diagnosis. The pooled average difference in IOP comparing patients with to those without diabetes was 0.18 mm Hg (95% CI 0.09 – 0.27, I^2 73.2%), while the pooled average increase in IOP associated with an increase in 10 mg/dL in fasting glucose was 0.09 mm Hg (95% CI 0.05 – 0.12, I^2 34.8%). Limited data on the association between HbA1c and metabolic syndrome with glaucoma precluded the calculation of pooled estimates.

Conclusions: Diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP.

INTRODUCTION

Glaucoma, the most common cause of irreversible blindness worldwide, represents a major public health problem [1]. The number of glaucoma patients in the US is expected to increase from 2.7 million in 2010 to 6.3 million in 2050 [2]. Elevated intraocular pressure (IOP) or ocular hypertension (OHT) is the only well-established modifiable risk factor for primary open-angle glaucoma (POAG), the most common form of glaucoma. There is thus considerable interest in identifying potentially modifiable risk factors for glaucoma in order to develop interventions that may reduce the incidence or improve the prognosis of the disease.

Diabetes mellitus has been suggested to causes microvascular damage and vascular dysregulation of the retina and the optic disc, increasing the susceptibility of the optic nerve head to damage in glaucoma [3–5]. Diabetes may also result in elevated IOP and increased risk of POAG by disrupting the trabecular meshwork function [6]. Diabetes has been proposed as a risk factor for elevated IOP and POAG, but epidemiological studies of the association between diabetes mellitus and glaucoma have been inconsistent [7–10] and the association is still controversial.

A meta-analysis published in 2004 evaluated the available literature on the association between diabetes mellitus and glaucoma [11]. This meta-analysis was based on 12 cross-sectional or case-control studies published before 2002. Several studies, including 6 longitudinal studies published in the past 10 years, have never been appraised systematically. Furthermore, there are no systematic reviews evaluating other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma. Our objective was thus to conduct a comprehensive and updated systematic review and meta-analysis to summarize the association between diabetes,

diabetes duration, metabolic syndrome, and glucose levels with the risk of glaucoma and with IOP levels in the general population.

METHODS

Search Strategy and Study Selection

Our systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [12]. The protocol for the systematic review was registered in the International Database of Prospectively Registered Systematic Reviews (PROSPERO number CRD42013005989). We searched MEDLINE and EMBASE to identify relevant studies. The search items were based on established terminology using MESH and EMBASE extensive search terms when possible. Keywords included diabetes mellitus, diabetes, metabolic syndrome, hyperglycemia, insulin resistance, hyperinsulinism, blood glucose, hemoglobin A1c, blood sugar, pancreas islet disease, intraocular pressure, intraocular tension, eye pressure, eye internal pressure, intraorbital pressure, ocular pressure, ocular tension, intraocular hypertension, intraocular tension, and glaucoma. The terms "diabetes" and "glaucoma" are general key terms that cover their subtypes in MEDLINE and EMBASE database searches. We also manually reviewed the reference lists from retrieved articles and identified additional relevant studies. The databases were searched for reports published through May 2013 with no language restrictions.

We aimed to identify all studies reporting an association between diabetes, metabolic syndrome, or glucose levels with glaucoma, IOP levels, or OHT in adults 18 years of age or older. The exclusion criteria were: (a) no original research (reviews, commentaries, editorials, or letters); (b) case reports or case series; (c) studies not conducted in humans or adults; (d)

studies conducted in population samples comprised only of patients with diabetes, metabolic syndrome, glaucoma or OHT at baseline; (e) studies not reporting glaucoma, IOP or OHT as outcomes; (f) studies not using diabetes, metabolic syndrome, blood glucose, or HbA1c as exposures; (g) studies mainly investigating drug effects or metabolism; (h) studies conducted in population samples comprised only of patients with specific conditions (e.g., hemodialysis, eye surgery) that limit their generalizability to general population samples. Since age is a strong risk factor for glaucoma and for diabetes development, we further excluded studies that did not adjust for age in the design or the analysis.

The study endpoints were POAG, IOP, and OHT. For studies that did not report POAG separately from other types of glaucoma, we used results for open angle glaucoma or glaucoma as endpoints. If more than one published paper reported on the same association within a study population, we selected the most recent publication or the publication with the longest follow-up. Studies reporting only correlation coefficients or point estimates of other measures of association without standard errors or any other estimates of statistical variability were included in the systematic review, but were excluded from the quantitative meta-analysis.

Data Extraction and Quality Assessment

Two authors (D.Z. and M.K.) independently reviewed all search results to identify eligible studies and abstracted data from selected articles. Discrepancies between reviewers were resolved by consensus or adjudication by the 3rd reviewer (E.G.). The following data were extracted from each study: publication year, country where the study was performed, study period, study size, sex and age of study participants, measure and range of exposure, methods for identification of type 2 diabetes, variables adjusted for in the analysis, and reported measures of association with corresponding standard errors or 95% CIs. We assessed study

quality using the methods described by Sanderson et al [13] and Viswanathan et al [14]. We examined the methods for selecting study participants, the criteria for defining exposures and outcomes, the risk of bias associated with different designs, the methods used to control for confounding, and potential conflicts of interest.

Statistical Analysis

We conducted separate meta-analysis for each combination of exposure (diabetes, diabetes duration, metabolic syndrome, and glucose levels) and outcome (glaucoma, IOP, and OHT) using random-effects meta-analyses to combine study-specific measures of association. For binary outcomes (glaucoma and OHT), the measures of association abstracted (odds ratios, incidence risk ratios, and hazard ratios) were combined together and referred to as relative risk (RR). We estimated the pooled average difference in IOP in mmHg comparing patients with and without diabetes and comparing patients with and without metabolic syndrome, as well as the pooled average difference in IOP associated with an increase in 10 mg/dL of serum glucose. Finally, we estimated the increase in glaucoma risk associated with a 1-year increase in diabetes duration compared to no diabetes by using a random-effects dose-response meta-analysis [15,16].

When a study reported several models for a given end point, we used the measure of association with the greatest degree of control for potential confounders. For studies reporting results separately by subgroup (e.g., men and women, diabetes with treatment and without treatment), we used the result for each group as independent results for the meta-analysis. For studies reporting standardized regression coefficients, we used the standard deviations reported for that population to recalculate unstandardized regression coefficients.

Between-study heterogeneity was quantified using the I^2 statistic. We also conducted sensitivity analyses omitting one study at a time to assess whether results were markedly affected by any single study. Publication bias was evaluated by funnel plots and by Egger's tests [17]. To examine potential sources of heterogeneity by study type (case-control, cross-sectional, longitudinal), location (Europe, America, Asia, other), year of publication (<2000, ≥2000), and exposure and outcome definitions we used meta-regression models with restricted maximum likelihood estimation of between-study variance. Meta-analyses were conducted with Stata version 12 (STATA Corp, College Station, TX).

RESULTS

We identified 47 studies including 2,981,342 individuals from 16 countries (**Supplementary Figure 1; Supplementary Table 1**). Sixteen studies were performed in North America, 15 in Asia, 11 in Europe, 2 in Australia, 1 in Africa, 1 in the Middle East, and 1 in the West Indies (**Table 1**). Thirty-two studies were cross-sectional, 9 were case-control, and 6 were longitudinal. Twenty-nine studies reported on the association between diabetes and glaucoma, 5 on diabetes duration and glaucoma, 2 on HbA1c and glaucoma, 1 on metabolic syndrome, glucose levels and glaucoma, 11 on diabetes and IOP levels, 6 on glucose and IOP levels, 6 on diabetes and OHT, and 1 on glucose and OHT. The definitions of the exposures and outcomes, and factors used for adjustment in each study are summarized in **Supplementary Tables 2 and 3**.

The prevalence of glaucoma ranged from 1.5 to 8.1%, and the prevalence of OHT ranged from 1.1 to 10.9% across studies. Among 29 studies that used glaucoma as outcome, 10 studies used characteristics of the optic disc, anterior chamber angle, optic nerve damage or visual field changes as diagnostic criteria, 10 studies also considered IOP as an additional

criteria, 4 studies used medical records, medication prescription records or medical database data, and 5 studies used self-reports. Among 17 studies using IOP levels as outcome, 7 measured IOP using Goldmann applanation tonometers and 10 measured IOP using non-contact tonometers.

Glaucoma

The pooled RR for glaucoma comparing patients with to those without diabetes was 1.48 (95% CI 1.29 – 1.71), with significant heterogeneity across studies (I^2 82.3%, $p < 0.001$) (**Figure 1**). The estimates from cross-sectional, case-control, and longitudinal studies were similar (RRs of 1.58, 1.44, and 1.37, respectively). The results were also similar by country, method for ascertainment of diabetes, criteria for defining glaucoma, and year of publication. However, the pooled RR for studies using exclusively POAG as outcome was 1.23 (95% CI 1.04 – 1.45), while the RR for studies using open angle glaucoma or glaucoma as outcome was 1.71 (95% CI 1.44 – 2.03). The pooled RRs obtained after omitting 1 study at a time ranged from 1.43 to 1.52. Egger's test for publication bias was statistically significant ($p < 0.001$) and funnel plots suggested that small studies were reporting stronger associations compared with larger studies, although large studies also reported positive associations.

Among five studies with dose-response data on the association of diabetes duration with glaucoma, the risk of glaucoma increased by 5% (95% CI 1 – 9%) for each year since diabetes diagnosis (**Figure 2**). In one study reporting the association between metabolic syndrome and POAG [22], the RR for POAG comparing participants with ≥2 metabolic syndrome components compared those with ≤1 components was 0.52 (95% CI 0.37 – 0.73). One cross-sectional study

reported the association between impaired blood glucose and POAG [31] with a RR of 1.2 (95% CI 0.8 – 1.8).

Intraocular pressure

The pooled average difference in IOP comparing patients with to those without diabetes was 0.18 mm Hg (95% CI 0.09 – 0.27), with substantial heterogeneity (I^2 72.3%) (**Figure 3**). The pooled estimates were not statistically different by study design, country, method for ascertainment of diabetes, method of IOP measurement, and year of publication (<2000, ≥2000). The pooled average differences in IOP comparing participants with to those without diabetes obtained after omitting one study at a time ranged from 0.14 to 0.34 mm Hg. Although Egger's test for publication bias was not significant, funnel plots suggested that small studies were reporting stronger associations compared with larger studies. Two additional studies reported regression coefficients without measures of variability and could not be incorporated in the pooled analysis. A study in Taiwan reported higher IOP levels among participants with diabetes compared to those without diabetes (regression coefficient 0.12 mm Hg, $p < 0.001$) while a study in Turkey reported lower IOP levels among participants with diabetes compared to those without diabetes (regression coefficient -0.13, $p < 0.001$) [32,33].

The pooled average increase in IOP associated with an increase in 10 mg/dL in fasting glucose was 0.09 mm Hg (95% CI 0.05 – 0.12, I^2 34.8%) (**Supplemental Figure 2**). The estimates ranged from 0.08 to 0.09 mm Hg after omitting one study at a time. Egger's test for publication bias was significant ($p = 0.01$) with small studies reporting stronger associations compared with larger studies.

Ocular hypertension

One case-control study, 4 cross-sectional studies and 1 longitudinal study reported data on the association between diabetes and OHT (**Supplemental Figure 3**). The pooled RR for OHT comparing participants with to those without diabetes was 1.52 (95% CI 1.11 – 2.09, I^2 53.1%). RR estimates were lower in case-control compared with cross-sectional studies or longitudinal studies (0.14, 1.69, and 1.38, respectively), but the results did not vary by year of publication, country, IOP threshold to determine OHT, or diabetes definition criteria. After omitting one study at a time, the pooled RRs varied from 1.37 to 1.62. Finally, one study reported data on the association between impaired fasting glucose (defined as ≥100 mg/dL) and OHT (RR 2.12, 95% CI 1.30 – 3.45) [34].

DISCUSSION

In this comprehensive meta-analysis, diabetes was associated with a significantly increased risk of glaucoma and with increased levels of IOP and OHT. Importantly, the association was also evident in longitudinal studies, which are less subject to bias than cross-sectional or case-control studies. We also identified positive associations between diabetes duration and the risk of glaucoma, and a weak association between fasting glucose levels and increased IOP levels. Finally, we identified a relative lack of research on the association between glucose biomarkers, prediabetes and metabolic syndrome with glaucoma. Given the high prevalence of these metabolic abnormalities, future studies should target this area of research to fully understand the implications of altered glucose metabolism on glaucoma risk.

The mechanisms relating diabetes to increased IOP are unclear. Increased IOP in diabetes may be due to hyperglycemia, which may induce an osmotic gradient that draws excess aqueous humor into the anterior chamber [35], and to autonomic dysfunction.

Hyperglycemia may also increase IOP by interrupting the trabecular meshwork function [6]. In addition, diabetes may increase corneal stiffness and central corneal thickness, which may artificially raise IOP readings [36–38]. The association between diabetes and IOP, however, was weak suggesting that the association between of diabetes and glaucoma may in part be independent of raised IOP. This is also supported by the fact that the association between diabetes and glaucoma in our meta-analysis was similar in studies that used IOP as criteria for defining glaucoma compared to those that did not use IOP.

Vascular mechanisms have been implicated to explain the increased risk of glaucoma in patients with diabetes irrespective of IOP levels. Diabetes causes microvascular damage and may affect vascular autoregulation of the retina and optic nerve [3,31,39]. Vascular damage can reduce blood flow and impair oxygen diffusion. Endothelial cell injury and dysfunction can reduce the autoregulatory capacity to protect against fluctuations of IOP and blood pressure [40–43], which could lead to relative hypoxia and to damage of the optic nerve head and of the retinal nerve fiber layer [38]. Furthermore, vascular changes in diabetes may increase the susceptibility of the retina to additional stress related to POAG or IOP elevation [5]. In addition to vascular changes, diabetes impairs physiological glial and neuronal function in the retina, which may increase the susceptibility of retinal ganglion cells to glaucomatous damage [4].

We also found that longer duration of diabetes was associated with higher risk of glaucoma. This robust association was consistent across cross-sectional, case-control and longitudinal studies and was independent of age, race, sex and other confounders controlled in the original studies. A longer duration of diabetes could impose prolonged damage to the glial and neuronal functions, leading to higher glaucoma risk. This finding further supports the need

for patients with longer duration of diabetes to adhere to optimal glaucoma screening exams and management.

As diabetes is a known risk factor for a variety of ocular diseases besides glaucoma, patients with diabetes are more likely to receive eye examinations. This may result in an overestimation of the association between diabetes and glaucoma, as the higher prevalence of glaucoma in patients with diabetes may be a reflection of more frequent ophthalmologic visits. In addition, it's also possible that retinal disease from diabetic retinopathy could lead to visual field defects, and could result in over-diagnosis of glaucoma in these studies. Indeed, the Beaver Dam Eye Study reported that the proportion of participants who had seen an ophthalmologist in the 2 years before enrollment was significantly higher in patients with diabetes compared to those without it [44]. Similarly, 22% of incident cases of glaucoma or OHT detected in diabetic patients in a retrospective cohort study were attributable to contact with medical services for diabetes screening [10]. However, other studies suggest that selection or information biases were unlikely to explain the association between diabetes and glaucoma. In the Nurses' Health Study, a longitudinal cohort study, participants with diabetes reported the same number of eye examinations on serial occasions as those without diabetes, and the prospective association between diabetes and glaucoma was unchanged when adjusting for factors that predicted more thorough eye examinations [45]. Also, in the Blue Mountains Eye Study, most of previously diagnosed cases of glaucoma had been diagnosed before the diagnosis of diabetes [7], indicating that the positive association between diabetes and risk of glaucoma cannot be completely explained by surveillance bias.

Several limitations need to be considered in the interpretation of our findings. First, there was substantial heterogeneity in the methods and quality of the original studies and the

methods used to ascertain exposure and outcomes varied widely across studies, likely contributing to the high degree of heterogeneity in the results. For instance, in our meta-regression analysis, studies using non-contact tonometers showed stronger associations between diabetes and IOP compared with studies using Goldmann applanation tonometers, the gold standard for measuring IOP. Second, there was also heterogeneity in the covariates adjusted for in each study. We attempted to limit the influence of uncontrolled confounders on this meta-analysis by excluding studies that did not adjust for age. However, some studies may still be affected by uncontrolled or residual confounding by factors such as ethnicity or central corneal thickness (CCT). For example, we found that studies that adjusted for CCT showed stronger associations between diabetes and IOP compared with studies that did not adjust for CCT ($P < 0.001$). Reassuringly, the findings of the meta-analysis were consistent in early studies, which tended to show more methodological limitations, and in more recent studies. Similarly, sensitivity analyses found that the results were consistent across study designs, location, and exposure and outcome assessment and definitions. This consistency adds weight to the internal validity of our findings.

Another concern was the lack of evidence of the effect modification by types of diabetes. The association between diabetes and the glaucomatous process may be different in type 1 diabetes, in which lack of insulin production leads to increased blood glucose, compared with type 2 diabetes, in which insulin resistance is the primary underlying mechanism. However, detailed information on the type of diabetes was not available in the original studies. In our meta-analysis, we found that patients with diabetes treated with insulin had a higher risk for glaucoma compared to patients with diabetes not treated with insulin [9,46–48] but we could not

identify if insulin was used in the context of type 1 or type 2 diabetes. Future studies should characterize the implications of the different types of diabetes on glaucoma risk.

Strengths of this meta-analysis included the large sample of studies combined, the evaluation of multiple diabetes-related exposures and glaucoma-related outcomes, and the inclusion of prospective studies, which provide natural estimates of incidence and temporal trends and can establish the temporal sequence required for causal inference.

In conclusion, we found that diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of POAG, and that diabetes and fasting glucose levels were associated with increased levels of IOP. As a consequence, the importance of glaucoma screening in patients with diabetes, particularly those with long-standing disease, should be underlined and could be considered when these patients are receiving routine diabetic eye screening.

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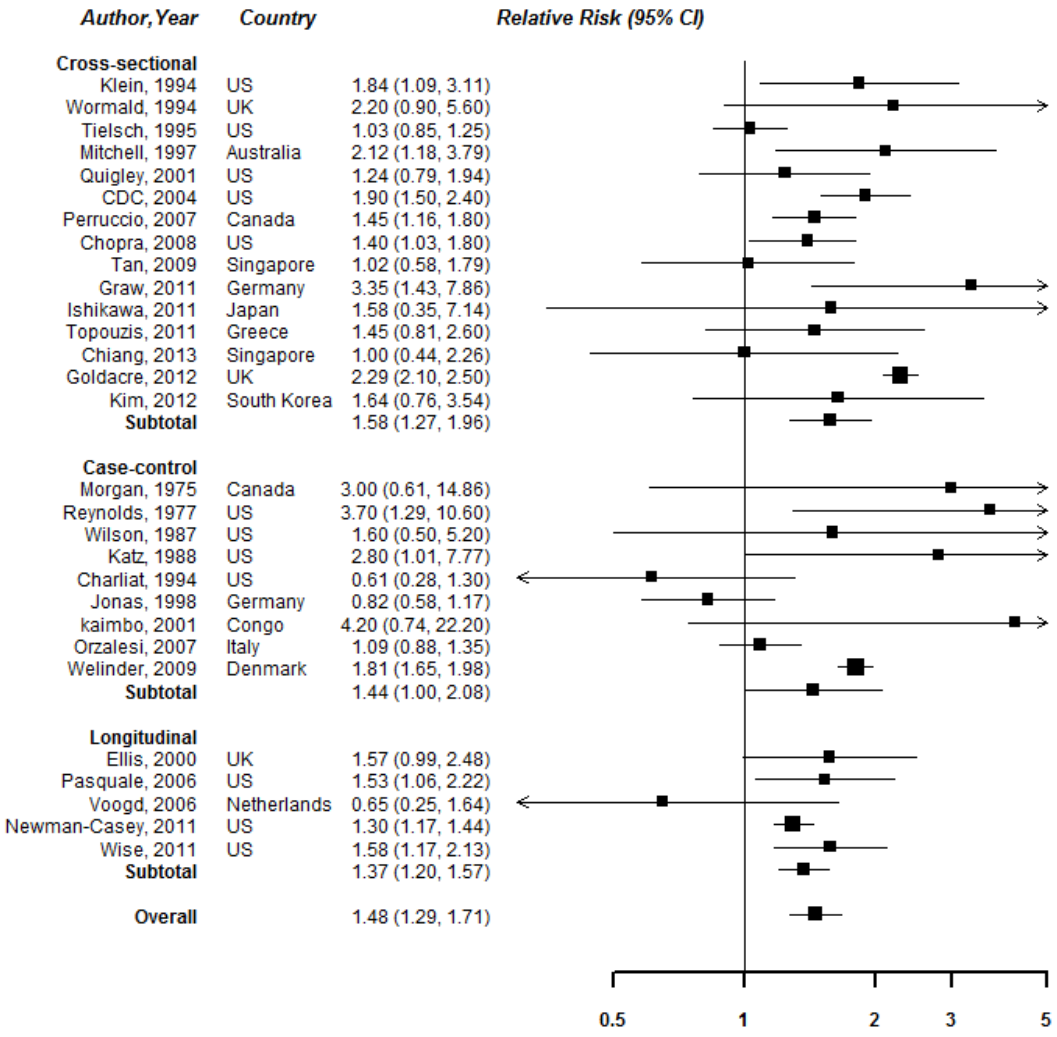
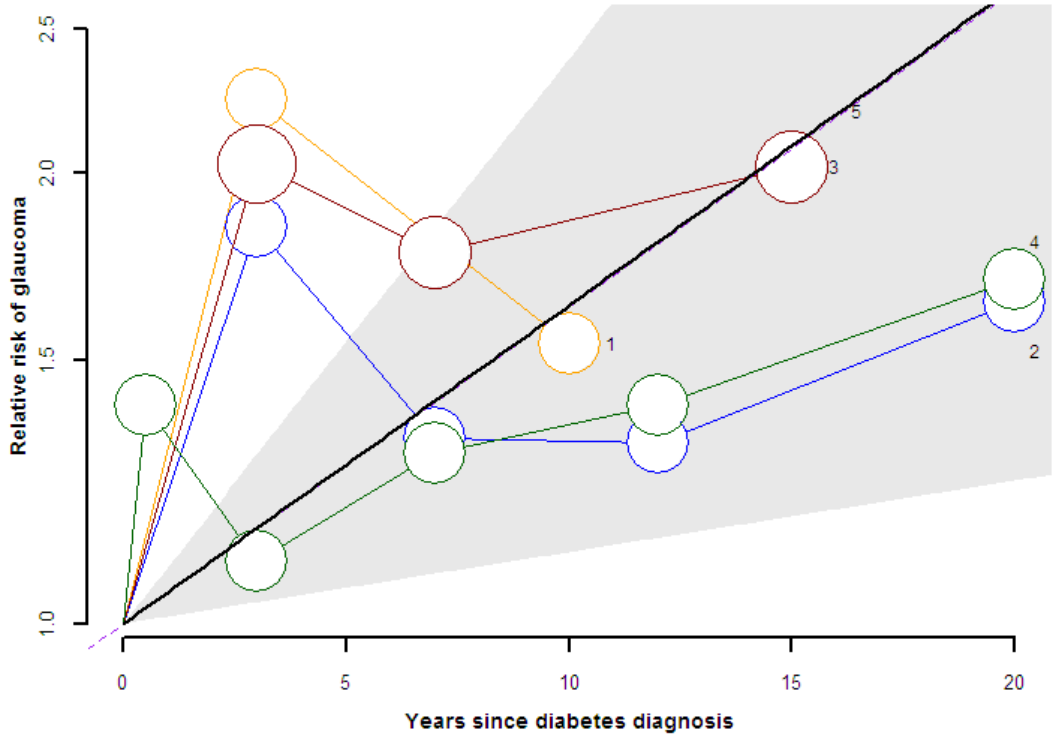
Figure 1. Relative risk for glaucoma comparing patients with to those without diabetes.



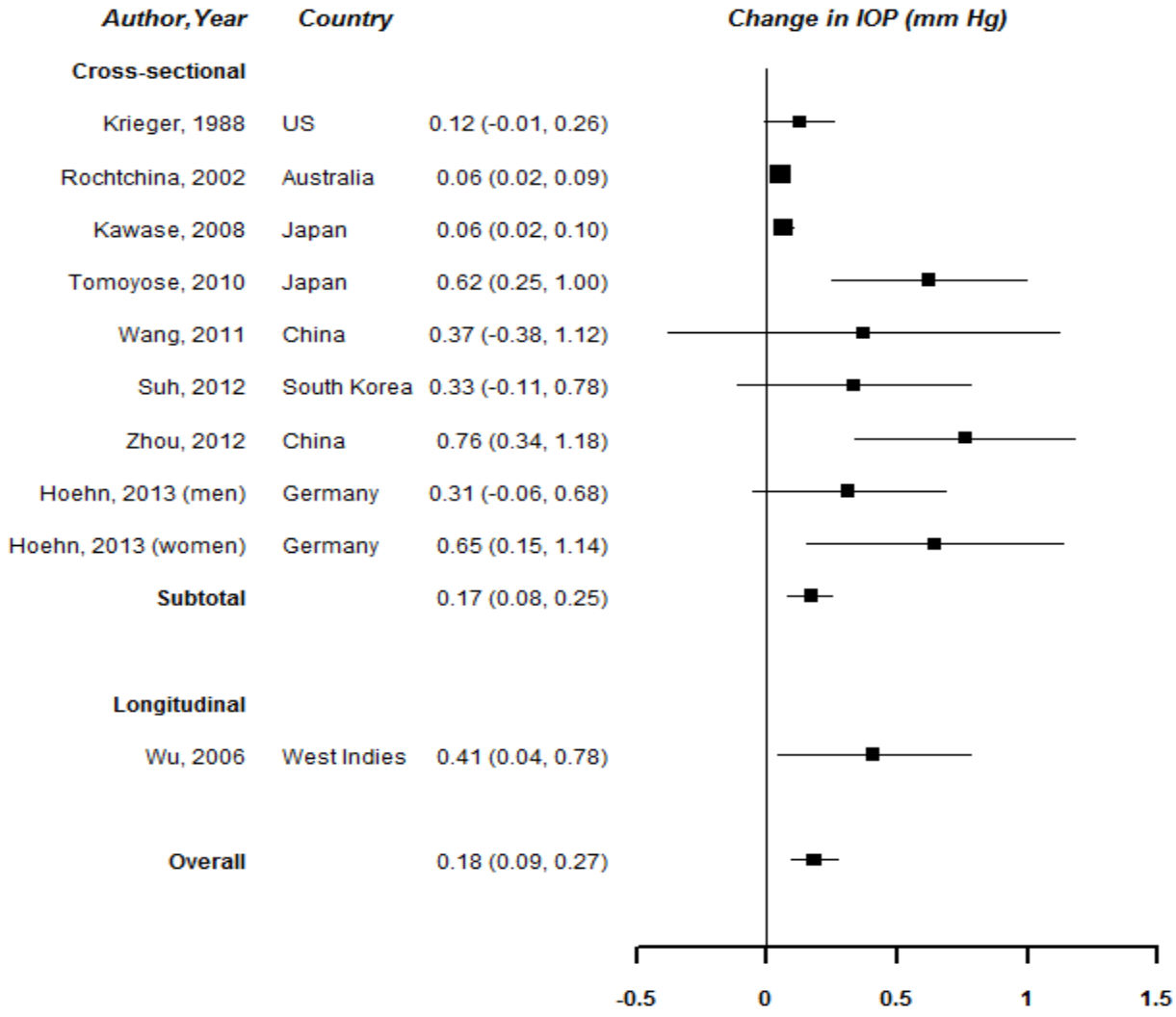
The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate. Horizontal lines represent 95% confidence intervals.

Figure 2. Relative risk for glaucoma with increasing duration of diabetes in dose-response meta-analysis.



Circle areas are inversely proportional to the variance of the log relative risks. The pooled linear risk trend (thick solid line) and its 95% confidence band (shaded region) were obtained using a random-effects dose-response meta-analysis. The individual studies were: 1: Pasquale et al., 2006; 2: Wise et al., 2011; 3: Welinder et al., 2009; 4: Chopra et al., 2008; 5: Chiang et al., 2013.

Figure 3. Difference in intraocular pressure comparing patients with to those without diabetes.



The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate. Horizontal lines represent 95% confidence intervals.

Supplemental Table 1. Characteristics of studies included in the meta-analysis.

First author, year	Country	Population	Setting	Sample size	Recruitment/ Follow-up year	Mean age or range (years)	Female, %	Mean IOP (mmHg)	Glaucoma (%)
Cross-sectional									
Leske, 1983	US	Framingham Heart Study and Framingham Eye Study	Community	2,433	1975	NA	NA	NA	NA
David, 1987	Israel	Asian, African, American or European origin	Health screening exam	2,594	1984	40-79	43.9	15.0	NA
Krieger, 1988	US	American Indians	Community	560	NA	12-89	66.4	NA	NA
Klein, 1994	US	Beaver Dam Eye Study	Community	4,926	1990	43-84	55.2	NA	2.2
Wormald, 1994	UK	African Caribbean subjects living in London	Community	873	1991	>35	64.1	NA	3.5
Tielsch, 1995	US	Baltimore Eye Survey	Community	5,308	1985-1988	≥40	60.3	NA	3.0
Mitchell, 1997	Australia	Blue Mountains Eye study	Community	3,654	1993	≥49	NA	NA	5.5
Quigley, 2001	US	Survey of Hispanics in Arizona	Community	4,774	1990	>40	61.2	Healthy: 15.6	NA
Rochtchina, 2002	Australia	Population-based survey	Community	3,654	1992-1994	≥49	56.6	DM: 16.5 Non-DM: 15.9	NA
CDC, 2004	US	National Health Interview Survey (NHIS)	Community	NA	2002	≥50	NA	NA	DM: 8.0 Non-DM: 4.3
Chen, 2005	Taiwan	Hospital based healthy subjects	Health screening exam	1,271	2001-2002	50.0	NA	13.6±2.9	NA
Lin, 2005	Taiwan	The Shihpai Eye Study	Community	1,292	1999-2000	≥65	40.0	12.9±3.1	NA
Oh, 2005	South Korea	Healthy visitors to health promotion center	Health screening exam	943	2003	Male: 15.7 Female: 15.1	NA	Male: 44.8 Female: 47.1	NA
Perruccio, 2007	Canada	National survey	Community	146,365	1994-95, 1996-97 and 1998-99	>20	NA	NA	Age ≥40: 2.7 Age ≥50: 3.9 Age ≥60: 5.6 Age ≥70: 7.7 Age ≥80: 11.0
Chopra, 2008	US	Los Angeles Latino Eye study	Community	5,894	2000-2003	54.9	58	NA	4.9
Kawase, 2008	Japan	Taijimi study	Community	2,597	2000	57.0	55.6	14.5	NA
Tan, 2009	Singapore	Singapore Malay Eye Study	Community	3,280	2004-2006	58.7	51.9	NA	3.2
Yazici, 2009	Turkey	Subjects admitted to clinics	Hospital outpatient clinic	850	2006	Male: 43.9 Female: 40.7	56.8	Male: 13.2 Female: 13.5	NA

Chang, 2010	Taiwan	National Taiwan University Hospital Yun-Lin Branch	Health screening exam	1,044	2006- 2008	MS: 55.2 No MS: 49.5	MS: 45.0 No MS: 50.0	MS: 15.1 No MS: 14.3	NA
Imai, 2010	Japan	Medical health checkup program at a general hospital	Health screening exam	14,003	2004-2008	14.8	41.5	NA	NA
Tomoyose, 2010	Japan	Kumejima Study	Community	2,838	2005	58.4	48.9	15.1	NA
Graw, 2011	Germany	KORA Eye Study	Community	2,593	1999	32-71	53.0	NA	1.5
Ishikawa, 2011	Japan	Residents participating in a community health checkup	Health screening exam	710	2007	>30	46.0	POAG: 17.2 No POAG: 15.0	3.7
Topouzis, 2011	Greece	Thessaloniki Eye study	Community	1,840	1999	POAG: 72.7 No POAG: 70.3	45.0	POAG: 72.7 No POAG: 70.3	4.5
Wang, 2011	China	Liwan Eye Study	Community	1,348	2003-2004	65.	57.3	15.2	NA
Goldacre, 2012	UK	Oxford Record Linkage Study (ORLS) and UK Linked Hospital Episode Statistics (LHES)	Hospital outpatient clinic	227,509	ORLS: 1963-1998 LHES: 1999-2010	0-80+	50.0	NA	1.6
Kim, 2012	South Korea	Local residents	Community	55 cases, 1,409 controls	2008	Case: 68.4 Control: 63.5	NA	Case: 15.7 Control: 13.4	NA
Lin, 2012	Taiwan	Medical health checkup program at a general hospital	Health screening exam	10,491	2008	Male: 49.2 Female: 50	42.4	Male: 13.7 Female: 13.8	NA
Suh, 2012	South Korea	Namil Study	Community	3,191	2005-2008	58.7	60.2	14.1	NA
Zhou, 2012	China	Handan Eye Study	Community	6,101	2006-2007	>30	53.0	15.0	NA
Chiang, 2013	Singapore	Singapore Malay Eye Study	Community	3,176	2004-2006	58.8	52.0	NA	NA
Hoehn, 2013	Germany	Gutenberg Heath Study	Community	4,335	2007-2008	54.7	48.9	14.0	NA
Case-control									
Morgan, 1975	Canada	Cases drawn from University of British Columbia and from a private practitioner	Hospital outpatient clinic	91 cases, 91 controls	NA	NA	NA	NA	NA
Reynolds, 1977	US	Sourthern College of Optometry Pathology Clinic	Hospital outpatient clinic	87 cases, 87 controls	1976	NA	NA	NA	NA
Wilson, 1987	US	General Eye Service of the Massachusetts Eye and Ear Infirmary	Hospital outpatient clinic	121 cases, 237 controls	1982-1984	NA	56.0	NA	NA
Katz, 1988	US	Wilmer Institute, Johns Hopkins Hospital	Hospital outpatient	NA	NA	NA	46.0	NA	NA

			clinic						
Charliat, 1994	US	Caucasian patients	Hospital outpatient clinic	175 cases, 175 controls	1993-1994	Case: 68.5 Control: 62.8	NA	Case: 18.4 Control: 15.4	NA
Jonas, 1998	Germany	Patients attending a hospital for diagnosis and treatment of glaucoma	Hospital outpatient clinic	529 cases, 660 controls	NA	Cases: 62.9 Controls: 63.1	NA	NA	NA
Kaimbo, 2001	Congo	Patients at an ophthalmology clinic	Hospital outpatient clinic	40 cases, 104 controls	1997	Case: 28–80 Control: 31–81	32.6	Case: 27.8 Control: 16.0	NA
Orzalesi, 2007	Italy	Patients from outpatient clinic	Hospital outpatient clinic	2,879 cases, 973 controls	NA	Case: 68 Control: 65	NA	Case: 16.5 Control: 15.4	NA
Welinder, 2009	Denmark	Danish National Registry of Patients (cases) and Civil Registration System (controls)	Community	5,991 cases, 59,910 controls	2001-2006	median age 70.4	58.4	NA	NA
Longitudinal									
Ellis, 2000	UK	Residents of the Tayside region, Scotland	Community	6631 DM subjects, 166144 non-DM subjects	1993-1995	Median in DM: 58 Median in non-DM: 66	NA	NA	Incidence in DM: 11 per 10,000 person-years Incidence in non-DM: 7 per 10,000 person-years
Pasquale, 2006	US	Nurses' Health Study	Work cohort	43732	1980-2000	DM: 61 No DM: 56	100	NA	Incidence 4.3 per 10,000 person-years
De Voogd, 2006	Netherlands	Rotterdam Study	Community	3837	Baseline 1990-1993, follow-up 1997-1999	65.7	60.3	15.0	8.1
Wu, 2006	West Indies	Barbados Eye Study	Community	2298	Data collection 1988- 1992, follow-up 1992-1997) and 1997-2003	55.1	61.1	17.5	NA
Newman-Casey, 2011	US	InVision Data Mart database	Community	2182315	2001-2007	54.5	57.0	NA	2.5
Wise, 2011	US	Black Women's Health Study	Community	32570	1995-2007	21-69	100	NA	Incidence 8.8 per 10,000 person-years

DM: Diabetes Mellitus; MS: Metabolic syndrome.

Supplemental Table 2. References of included studies.

Cross-sectional

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Supplemental Table 3. Exposure and outcome ascertainment in included studies.

First author, year	Exposure	Exposure definition/measurement	Outcome	Outcome definition/measurement
Cross-sectional				
Leske, 1983	DM	NA	OHT	OHT: IOP > 21 mm Hg without symptoms of POAG IOP: Goldmann applanation tonometer
David, 1987	DM	Self-report	OHT	OHT: IOP≥21 mm Hg without symptoms of POAG IOP: Goldmann applanation tonometer
Krieger, 1988	DM, blood sugar	Diabetes Self-report; blood sugar randomly drawn	IOP	Goldmann applanation tonometer
Klein, 1994	DM	History of Diabetes treated with insulin or oral hypoglycemia agents and/or diet or glycosylated hemoglobin level >2 SD above the mean of the relevant age-sex group and a casual blood sugar level >11.1 mmol/l	Glaucoma	Glaucoma: Visual field defect, cup-to-disc ratio, IOP≥22, history of taking drops for or having surgery for glaucoma IOP: Goldmann applanation tonometer
Wormald, 1994	DM, FBG	History of diabetes treatment including diet alone, tablets and insulin dependence or a random blood sugar tested on a glucose check device with BM sticks above 15 mmol.	Glaucoma	Already diagnosed as glaucoma (confirmed at survey) and receiving treatment or newly diagnosed during the survey and confirmed on follow-up assessment at Moorfields Eye Hospital on agreement by two ophthalmologists.
Tielsch, 1995	DM	Self-report	POAG	Glaucomatous optic nerve damage and optic disc ratio
Mitchell, 1997	DM	Self-report or FBG ≥7.8 mmol/L	Glaucoma, OHT	Glaucoma: questionnaire, optic disc cupping and rim thinning, and visual field defects. Ocular hypertension: IOP≥22 after excluding cases of rubeotic, secondary or angle-closure glaucoma.
Quigley, 2001	DM	Self-report or HbA1c ≥7%	OAG	OAG: 1 of the following sets of findings in at least 1 eye and had to have an open angle by gonioscopy: (1) 1 eye with optic disc damage and a visual field in the same eye; (2) at least 1 eye with a cup-disc ratio ≥99.5th percentile for the population; and (3) visual acuity was in the legal blindness category and IOP ≥99.5 percentile for the population. IOP: Goldmann applanation tonometer
Rochtchina, 2002	DM	History or FBG ≥7.0 mmol/L	IOP	Goldmann applanation tonometer
CDC, 2004	DM	Self-report	Glaucoma	Self-report
Chen, 2005	FBG (mg/dl)	Blood drawn	IOP	Noncontact tonometer
Lin, 2005	DM	Self-report	IOP	Noncontact tonometer
Oh, 2005	FBG (mg/dl)	Blood drawn	IOP	Noncontact tonometer
Perruccio, 2007	DM	Self-report	Glaucoma	Self-report
Chopra, 2008	DM, DM duration, impaired glucose, impaired	DM: history of treatment for DM, HbA1c ≥7.0%, random blood glucose ≥200 mg/dL. Impaired glucose: random blood glucose ≥200 mg/dL. Impaired HbA1c: HbA1c ≥7.0%.	OAG	OAG: Open angle and a glaucomatous visual field abnormality and/or evidence of glaucomatous optic disc damage in at least one eye.

	HbA1c			
Kawase, 2008	DM	Self-report	IOP	Goldmann applanation tonometer
Tan, 2009	DM, metabolic syndrome, glucose, HbA1c	DM: physician diagnosis of DM and use of diabetes medications or non-FBG ≥200 mg/dL or. Metabolic syndrome: at components were defined as follows: for obesity, BMI of 25 or greater; for hypertriglyceridemia, triglyceride level of 1504 mg/dL or greater; for low level of highdensity lipoprotein cholesterol, a value less than 38.7 mg/dL in men and less than 50.3 mg/dL in women; for high blood pressure, 130/85 mm Hg or greater or use of blood pressure medication; and for Diabetes mellitus, as defined earlier	POAG	Glaucoma: IOP >21 mm Hg, gonioscopic findings of closed or occludable angles, presence of peripheral anterior synechiae, cup-disc ratio >0.6, disc asymmetry with cup-disc ratio >0.2, abnormal deposits on pupil margin consistent with pseudoexfoliation syndrome, pigment deposition on the cornea consistent with pigment dispersion syndrome, and known glaucoma. POAG: glaucoma without any evidence of narrow angles, primary angle-closure glaucoma, or a secondary cause (eg, abnormal anterior segment deposits or iris neovascularization). IOP: Goldmann applanation tonometer.
Yazici, 2009	DM, FBG	Self-report	IOP	Non-contact pneumotonometer
Chang, 2010	FBG (mg/dl)	Blood-drawn	IOP	Non-contact tonometer
Imai, 2010	elevated FBG	FBG≥5.56 mmol/l	OHT	OHT: IOP>21 mm Hg without optic-disc abnormalities or history of receiving anti-glaucoma therapy IOP: non-contact tonometer
Tomoyose, 2010	DM	Self-report	IOP	Goldmann applanation tonometer
Graw, 2011	DM	Self-report	Glaucoma	Self-report
Ishikawa, 2011	DM	HbA1c⩾5.8% and/or previous diagnosis of DM	POAG	POAG: optic disk appearance, including cup-to-disk ratio, rim width, nerve fiber layer defect, the visual field test, and clinical records
Topouzis, 2011	DM	Self-report	POAG	Glaucoma: Presence of thinning or notching or cup-to-disc ratio asymmetry of 0.2, and a confirmed threshold glaucomatous visual field defect, or a strong clinical judgment in favor of the presence of glaucoma POAG: glaucoma and an open, normal-appearing anterior chamber angle and the absence of other secondary causes of glaucoma in either eye.
Wang, 2011	DM	Self-report history or previous medication use	IOP	Handheld tonometer
Goldacre, 2012	DM	Medical records	Glaucoma	Hospital record
Kim, 2012	DM	Self-report	POAG	IOP levels, anterior chamber depth, gonioscopic results, appearance of the optic disc and retinal nerve fiber layer, and perimetric results
Lin, 2012	FBG, Postprandial sugar (mg/dl)	Postprandial blood sugar levels were also examined approximately 2 h after breakfast on the same day	IOP	Non-contact tonometer
Suh, 2012	DM	Self-report	IOP	Goldmann applanantion tonometer
Zhou, 2012	DM	Self-report	IOP	Perkins handheld applanation tonometer
Chiang,	DM, DM	Blood glucose ≥11.1 mmol/l, use of diabetic medication or	POAG,	Glaucoma: IOP > 21 mm Hg, gonioscopic findings of closed or occludable angles, presence of

2013	duration	a physician diagnosis	OHT	peripheral anterior synechiae, cup-disc ratio > 0.6, disc asymmetry with cup-disc ratio>0.2, abnormal deposits on pupil margin consistent with pseudoexfoliation syndrome, pigment deposition on the cornea consistent with pigment dispersion syndrome, and known glaucoma POAG: glaucoma without evidence of narrow angles, primary angle-closure glaucoma, or a secondary cause. OHT: IOP>21 mmHg IOP: Goldmann applanation tonometer
Hoehn, 2013	DM	Definite diagnosis and treatment, a blood glucose>126 mg/dl after overnight fasting≥8 hours or a blood glucose >200 mg/dl after a fasting≥8 hours.	IOP	Noncontact tonometer
Case-control				
Morgan, 1975	DM	NA	POAG, OHT	POAG: IOP > 21 mm Hg with optic disc change and field defect OHT: IOP > 21 mm Hg without symptoms of having POAG IOP: NA
Reynolds, 1977	DM	Clinical records	POAG	POAG: IOP > 21 mm Hg with optic disc change and field defect IOP: NA
Wilson, 1987	DM	Self-report	POAG	POAG: IOP>21, optic disc changes and representative field defects IOP: NA
Katz, 1988	DM	Self-report	POAG	POAG: IOP>21, glaucomatous visual field defects on at least two occasions IOP: Goldmann applanation tonometer
Charliat, 1994	DM	Self-report	POAG	Glaucomatous cupping in at least one eye
Jonas, 1998	DM	Antidiabetic diet, medication, or if blood sugar were above the normal range.	POAG	An open anterior chamber angle and glaucomatous changes of the optic nerve head and/or glaucomatous visual field defects.
kaimbo, 2001	DM	Self-report	OAG	OAG: IOP≥21 mm Hg, vertical cup/disc ratio, visual field defect. The diagnosis of OAG was based on at least two of the three criteria in at least one eye. IOP: Goldmann applanation tonometer
Orzalesi, 2007	DM	NA	POAG	Presence of a glaucomatous optic disc, or glaucomatous visual field changes, and open angle (grades 2–4, Shaffer's classification).
Welinder, 2009	DM, DM duration	Prescription and hospital data.	Glaucoma	Filling three or more prescriptions for a glaucoma medication over 365 days or less.
Longitudinal				
Ellis, 2000	DM	Diabetes Audit and Research in Tayside Study (DARTS) validated regional Diabetes register	POAG, OHT	Glaucoma: encashment of community prescriptions and the statutory surgical procedure coding database. OHT: IOP>21 mm Hg
Pasquale, 2006	DM, DM duration	Self-report	POAG	Gonioscopy was performed and that the angles were not occludable in either eye; slit-lamp biomicroscopy showed no indication in either eye of pigment dispersion syndrome, exfoliation syndrome, trauma, uveitis, or rubeosis; and VF defects consistent with glaucoma.
De Voogd, 2006	DM	Use of antidiabetic medication and/or a random or post load glucose value≥11.1 mmol/l	OAG	Presence of glaucomatous optic neuropathy and glaucomatous visual field loss, an open anterior chamber angle and no history or sign of angle-closure or secondary glaucoma.
Wu, 2006	DM	Self-report	IOP	Goldmann applanation tonometer

Newman-Casey, 2011	DM	1 or more of the following ICD-9 codes: 250.0, 250.00, 250.01, 250.02, 250.03, 250.1, 250.10,250.11, 250.12, 250.13, 250.2, 250.20, 250.21, 250.22, 250.23, 250.3, 250.30,250.31, 250.32, 250.33, 250.4, 250.40, 250.41, 250.42, 250.43, 250.5, 250.50,250.51, 250.52, 250.53, 250.5, 250.50, 250.51, 250.52, 250.53, 250.6, 250.60,250.61, 250.62, 250.63, 250.7, 250.70, 250.71, 250.72, 250.73, 250.8, 250.80,250.81, 250.82, 250.83, 250.9, 250.90, 250.91, 250.92, 250.93, 362.01, 362.92, 362.03, 362.04, 362.05, 362.06, 362.07	OAG	1 or more of the following ICD-9-CM codes: 365.1, 365.10, 365.11, 365.12, and 365.15.
Wise, 2011	DM, DM duration	Self-report	POAG	Self-report

DM: Diabetes Mellitus; FBG: Fasting blood glucose; OGTT: Oral glucose tolerance test; POAG: Primary open-angle glaucoma; OHT: Ocular hypertension.

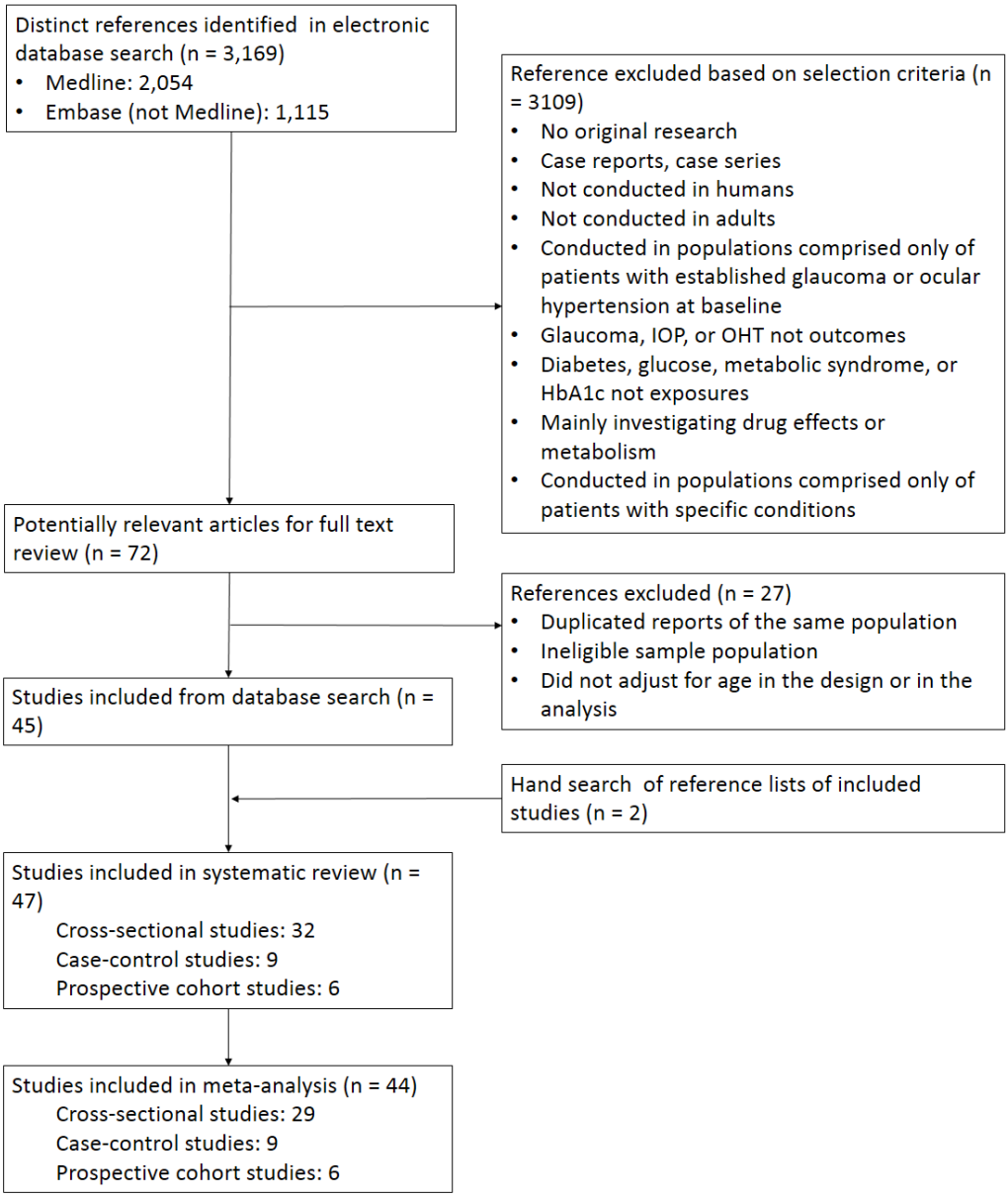
Supplemental Table 4. Covariates adjusted for in each study.

First author, year	Covariates
Cross-sectional	
Leske, 1983	Age, sex, hypertension
David, 1987	Age
Krieger, 1988	Age, sex, weight index, BP, blood sugar, degree Indian
Klein, 1994	Age, sex
Wormald, 1994	Age, sex, hypertension, skin color, place of birth
Tielsch, 1995	Age
Mitchell, 1997	Age, gender
Quigley, 2001	Age
Rochtchina, 2002	Age, SBP, family history of Glaucoma, myopia
CDC, 2004	Demographic characteristics
Chen, 2005	Age, SBP,DBP, tg, sex
Lin, 2005	Age, SBP, sex, alcohol
Oh, 2005	Age, sex, weight, height, BMI, waist circumference, body fat, BP, LDL, HDL, triglycerides, fasting insulin, and/or the insulin sensitivity indices
Perruccio, 2007	Age, sex, income, education, and all chronic conditions
Chopra, 2008	Age, gender, and IOP
Kawase, 2008	Age, sex, BMI, SBP, DBP, smoking, CCT, the radius of corneal curvature, SE
Tan, 2009	Age, sex, education, smoking, CCT and diabetic treatment
Yazici, 2009	Age, sex, refractive status, CCT, hypertension, and hyperlipidemia
Chang, 2010	Age, sex, DBP, triglycerides
Imai, 2010	Age, temperature, abdominal circumference, BP, HDL cholesterol, triglyceride
Tomoyose, 2010	Age, gender, BMI, corneal curvature, SBP, DBP, smoking, corneal curvature, CCT, anterior chamber depth, axial length, average Shaffer angle width grade
Graw, 2011	Age, sex
Ishikawa, 2011	Age, gender, DBP, IOP, and ocular perfusion pressure.
Topouzis, 2011	Age, IOP, BP, Coronary artery bypass or vascular surgery, myopia
Wang, 2011	Age, sex
Goldacre, 2012	ORLS: Age, sex, time-period, district of residence in the ORLS datasets LHES: Age, sex, time-period, region of residence and deprivation score associated with patients' area of residence
Kim, 2012	Age, sex, hypertension, thyroid disease, family history of Glaucoma, IOP
Lin, 2012	Age, sex, BMI, DBP, TG, hs_CRP
Suh, 2012	Age, sex, area, CCT, RE, cup to disc ratio, family history of Glaucoma, CVD, smoking
Zhou, 2012	Age, sex, smoking, mean arterial pressure, CCT, BMI, family history of Glaucoma, SE
Chiang, 2013	Glaucoma: Age, gender OHT: Age, sex, income, HbA1c, hypertension, history of stroke and myocardial infarction, hyperlipidemia, BMI and smoking
Hoehn, 2013	Age, iris color, CCT, waist-to-hip ratio, smoking, hypertension, dyslipidemia
Case-control	
Morgan, 1975	Age, sex, education, income
Reynolds, 1977	Age, sex and race
Wilson, 1987	Age, sex, race, family history of POAG, sbp, smoking, myopia, radiation exposure, metal exposure, and reason for attendance
Katz, 1988	Age, race and sex

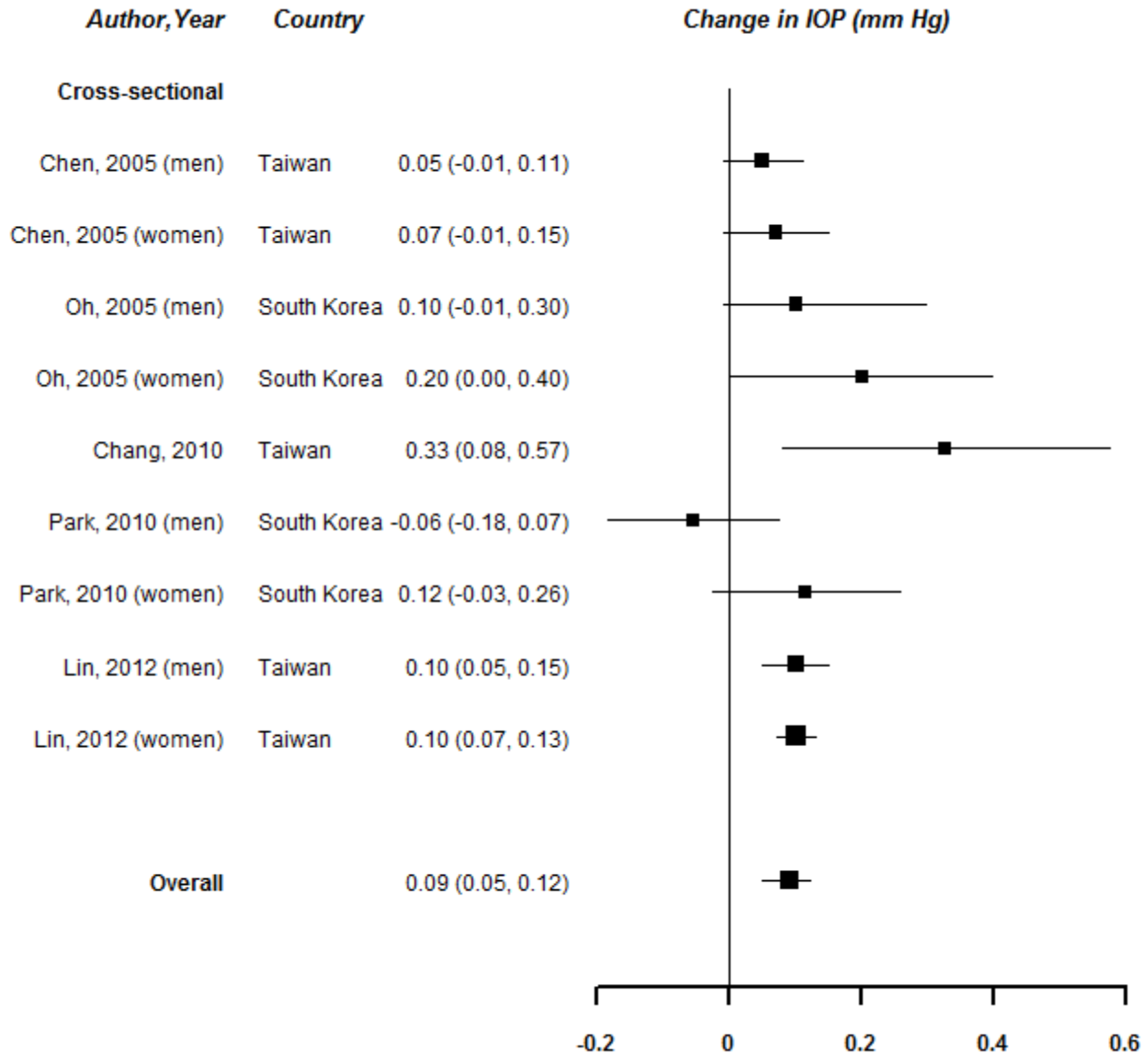
Charliat, 1994	Age, sex, type of health care
Jonas, 1998	Age
Kaimbo, 2001	Age, BMI, hyperopia, Mongo ethnic group, Rice
Orzalesi, 2007	Age
Welinder, 2009	Age, sex, and residence. CVD, hypertension, thyroid disease, migraine, autoimmune disorders, alcoholism-related diagnoses, cataract, retinal detachment and uveitis
Longitudinal	
Ellis, 2000	Age
Pasquale, 2006	Age
De Voogd, 2006	Age, gender, follow-up time, IOP, IOP–lowering treatment, BMI, systemic hypertension
Wu, 2006	Age, sex, hypertension, and baseline IOP
Newman-Casey, 2011	Age, sex, race, education level, house-hold net worth, region of residence at the time of medical plan enrollment, cataract, pseudophakia or aphakia, macular degeneration, diabetic retinopathy, hypotension, sleep apnea syndrome, migraine headache, Charlson comorbidity index, and each of the other metabolic syndrome
Wise, 2011	Age, questionnaire cycle, education, smoking, alcohol, hypertension, exercise, and energy intake

BMI: body mass index; CCT: central corneal thickness; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: Diabetes Mellitus; FBG: Fasting blood glucose; MS: Metabolic syndrome; RE: refractive error; SES: social economic status; SE: spherical equivalent; SBP: systolic blood pressure.

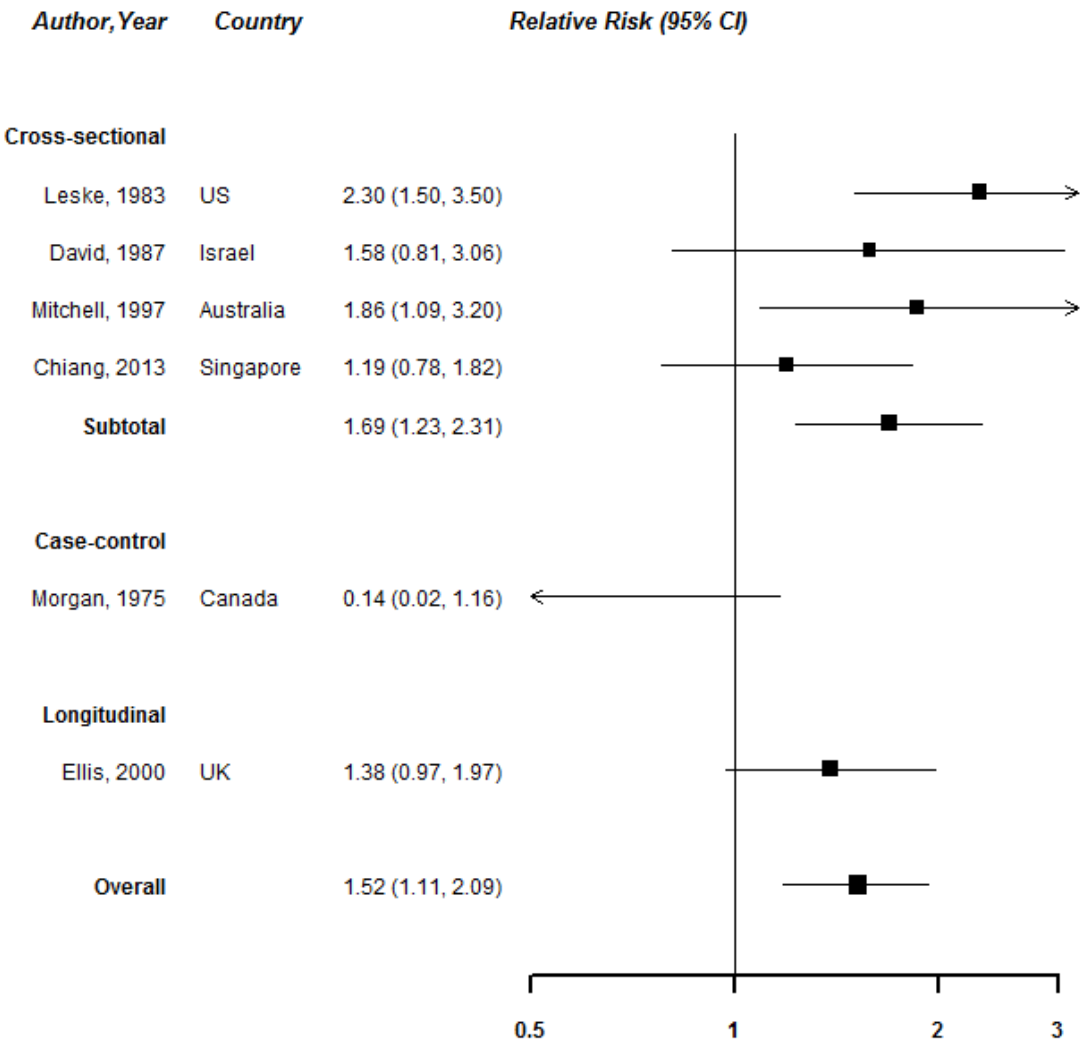
Supplemental Figure 1. Flow diagram of study selection process.



Supplemental Figure 2. Change in intraocular pressure associated with a 10 mg/dL increase in fasting serum glucose.



Supplemental Figure 3. Relative risk for ocular hypertension comparing participants with to those without diabetes.



CHAPTER 4

DIABETES, GLUCOSE METABOLISM, AND GLAUCOMA: THE 2005 – 2008 NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

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Running title: Diabetes and glaucoma.

Key words: Diabetes; fasting glucose; glaucoma; HbA1c; HOMA-IR; metabolic syndrome; pre-diabetes.

ABSTRACT

Background: Diabetes may affect vascular autoregulation of the retina and optic nerve and may be associated with an increased risk of glaucoma, but the association of prediabetes, insulin resistance, markers of glucose metabolism with glaucoma has not been evaluated in general population samples.

Objective: To examine the relation between diabetes, pre-diabetes, metabolic syndrome and its components and the levels of fasting glucose, HbA1c and HOMA-IR with the prevalence of glaucoma in the general U.S. population.

Methods: Cross-sectional study of 3,299 adult men and women from the 2005 – 2008 National Health and Nutrition Examination Survey (NHANES). The presence of diabetes, prediabetes, the metabolic syndrome and its individual components and biomarkers of glucose metabolisms were based on standardized questionnaire and physical exam data and laboratory tests. The history of glaucoma was assessed through questionnaire during the home interview.

Results: Diabetes was strongly associated with prevalent glaucoma. In fully adjusted models, the odds ratio for glaucoma comparing participants with diabetes with participants in the reference group with neither pre-diabetes nor diabetes was 2.12 (95% CI: 1.23, 3.67). The corresponding odd ratio comparing participants with pre-diabetes to those in the reference group was 1.01 (95% CI: 0.57, 1.82). Patients with 5 or more years of diabetes duration had an OR for glaucoma of 3.90 (95% CI: 1.63, 9.32) compared with patients with <5 years of diabetes duration. We also found a hockey-stick shaped associations between biomarkers of glucose metabolisms and the prevalence of glaucoma.

Conclusions: Diabetes was associated with higher risk of glaucoma. Participants without diabetes but at the higher levels of fasting glucose, fasting insulin, HbA1c and HOMA-IR spectrum may also be at greater risk of glaucoma.

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INTRODUCTION

Diabetes is a common chronic disease worldwide with a dramatic increase in incidence in recent decades [1]. Diabetes is associated with a variety of ocular complications, including retinopathy, cataracts, uveitis and neovascularization [2]. Several studies also suggested that diabetes may be associated with an increased risk of glaucoma [3–5]. A meta-analysis of 12 studies published prior to 2004 found a pooled odds ratio for primary open angle glaucoma (POAG) comparing participants with diabetes to those without diabetes of 1.50 (95% confidence interval [CI] 1.16 – 1.93) [6], but there was significant heterogeneity and many studies reported non-significant associations [7–11] or negative point estimates [12–15].

Other abnormalities of glucose metabolism, including pre-diabetes, metabolic syndrome, insulin resistance, and elevated fasting glucose or hemoglobin A1c (HbA1c), may also be associated with glaucoma risk, but few studies have examined this issue, with conflicting results [16–19]. The objective of this study was thus to examine the relation between diabetes, pre-diabetes, metabolic syndrome, and markers of glucose metabolism with the prevalence of glaucoma in the U.S. population aged 40 years and older using data from the 2005–2008 National Health and Nutrition Examination Survey (NHANES).

RESEARCH DESIGN AND METHODS

Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative study of the non-institutionalized US population, obtained by using a stratified multistage probability design with planned oversampling of certain age and minority groups. NHANES is conducted by the National Center of Health Statistics of the Centers for Disease

Control and Prevention [20]. Information on glaucoma prevalence was only available in the 2005 – 2008 survey waves, and fasting glucose and insulin levels were only assessed in participants who were examined in the morning session. Therefore, we restricted our analysis to NHANES 2005 – 2008 participants 40 years of age or older who were examined in the morning session (N = 3,299). We then excluded 255 participants whose duration of fasting was < 8 h (if they didn't have a prior diagnosis of diabetes), 17 participants who had missing information regarding glaucoma in the questionnaire, and 1 participant with missing data in all exposure variables of interest. The final analysis was based on 3,026 participants (1,501 men and 1,525 women).

The 2005 – 2008 NHANES study protocols were approved by the Institutional Review Board of the National Center for Health Statistics. Written informed consent was obtained from all participants.

Measurements

NHANES included a standardized questionnaire administered at home by a trained interviewer and a detailed physical examination at a mobile examination center. Self-reported glaucoma status was ascertained via the question "Have you ever been told by an eye doctor that you have glaucoma, sometimes called high pressure in your eyes?" Demographic information, education, smoking history, physical activity levels, alcohol consumption, medication use, health history, and age of diabetes onset were also determined by self-report. Leisure-time physical activities were coded and classified according to the rate of energy expenditure (<7.5, 7.5 to <15, and ≥15 metabolic equivalent hours per week) to correspond with cut points in the 2008 US federal physical activity guidelines [21] and the 2010 World Health Organization (WHO) guidelines. [22] Height, weight, and blood pressure were measured

at the mobile examination center using standard procedures by trained health technicians [23,24]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Fasting times ranged from 0.53 to 40.5 hours. Fasting blood samples were centrifuged and plasma was separated within 30 minutes from blood collection. Plasma glucose was analyzed using the hexokinase method in a Roche/Hitachi 911 (Roche Diagnostics, 9115 Hague Road, Indianapolis, IN) and a Roche Modular P chemistry analyzer (Roche Diagnostics, 9115 Hague Road, Indianapolis, IN) in 2005 – 2006 and 2007 – 2008, respectively [25]. Fasting insulin was analyzed using Merocodia Insulin ELISA kits [20]. HbA1c was measured using high-performance liquid chromatography on an A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, Ca) in 2005 – 2006 and on an A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, Ca) in 2007 – 2008 [26].

Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL, an HbA1c level ≥ 6.5%, a self-reported diagnosis of diabetes (excluding gestational diabetes mellitus), or a self-report of current insulin or diabetes medication use. Pre-diabetes was defined in participants without diabetes as a fasting plasma glucose level between 100 mg/dL and 126 mg/dL, an HbA1c level between 5.7 and 6.5%, or a self-report of a diagnosis of borderline diabetes. Additional analyses were conducted defining diabetes and pre-diabetes using fasting plasma glucose or HbA1c criteria separately. Diabetes duration was calculated as the age at interview minus the age at the first time that the participant was told to have diabetes.

Metabolic syndrome components were defined as detailed in the Adult Treatment Panel (ATP) III report [27]: 1) waist circumference ≥ 102 cm in men and ≥ 88 cm in women; 2) fasting triglycerides ≥ 150 mg/dL; 3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women;

4) blood pressure ≥ 130/85 mm Hg; and 5) fasting glucose ≥ 110 mg/dL or use of antidiabetic medication. Persons with at least 3 of these characteristics were defined as having metabolic syndrome. We also calculated the homeostatic model assessment of insulin resistance (HOMA-IR) as fasting glucose (mg/dl) x fasting Insulin (uU/mL) / 405 and defined insulin resistance as HOMA-IR > 2.6 [28].

Statistical analysis

All statistical analyses were performed using NHANES weights and *svy* commands in STATA (version 12; Stata Corp., College Station, TX) to account for the complex multistage probability sampling design. Analyses of fasting glucose, fasting insulin, HOMA-IR, and HbA1c levels were restricted to participants not taking insulin or antidiabetic medications (N = 2,509). Fasting glucose, fasting insulin, HOMA-IR, and HbA1c levels were categorized into quartiles based on the weighted population distribution.

We used multivariable logistic regression models to calculate odds ratios (OR) and 95% CI for the prevalence of glaucoma associated with glucose metabolism variables. Diabetes and pre-diabetes were included as exposures in the same model, and we fitted separate models for diabetes duration, metabolic syndrome and each its components, insulin resistance, fasting glucose, fasting insulin, HOMA-IR, and HbA1c. For each exposure, we used 3 models with progressive degrees of adjustment. Initial models were crude and then we adjusted for age, sex (male, female) and race/ethnicity (non-Hispanic, white, non-Hispanic black, Mexican American, and other). Finally, fully adjusted models further included education (< high school, high school, > high school), smoking (never, former, current), average physical activity level (low, medium, vigorous), alcohol drinking (< 1 drink/week, 1 to < 3 drinks/week, ≥3 drinks/week) and BMI (continuous).

For dose-response analyses of the associations of fasting glucose, fasting insulin, HOMA-IR, and HbA1c levels with the prevalence of glaucoma, we calculated OR and 95% CI comparing quartiles 2 – 4 with the first quartile in categorical analyses, as well as OR and 95% CI comparing the 80th to the 20th percentiles of markers of glucose metabolism modeled as log-transformed continuous variables. In addition, we used restricted cubic spline models with knots at the 10th, 50th and 90th percentiles of the distribution of fasting glucose, fasting insulin, HOMA-IR, and HbA1c concentrations to provide a smooth yet flexible description of the shape of dose-response relationship. Tests for non-linear trends computed by log likelihood ratio tests comparing nested models with and without non-linear spline terms.

RESULTS

The study population had a weighted mean (SE) age of 57.0 (0.4) years (**Table 1**). The prevalence of diabetes, pre-diabetes, metabolic syndrome, and insulin resistance were 17.1, 49.0, 32.1, and 43.4%, respectively, and the prevalence of glaucoma was 4.2% (95 % CI 3.3 – 5.3%). The average duration of diabetes was 11.8 years. Participants with prevalent glaucoma were more likely to be older, non-Hispanic black, less educated, and had higher waist circumference, blood pressure, fasting glucose and HbA1c levels (**Table 1**) and to have a significantly higher prevalence of diabetes, elevated blood pressure, and elevated fasting glucose (**Table 2**).

The prevalence of glaucoma in participants with diabetes, with pre-diabetes, and without diabetes or pre-diabetes was 9.5, 3.5, and 2.6%, respectively ($P < 0.001$). In age-, sex-, and race / ethnicity-adjusted models, the OR for glaucoma comparing participants with diabetes to those without diabetes or pre-diabetes was 2.09 (95% CI 1.11 to 3.92) (**Table 3**). The corresponding OR in fully adjusted models was 1.80 (95% CI 0.93 to 3.47). The association of

diabetes with glaucoma prevalence was stronger when the definition of diabetes was based on either fasting glucose or HbA1c levels only, with ORs of 2.12 (95% CI 1.23 to 3.67) and 2.10 (95% CI 1.19 to 3.71), respectively. The fully adjusted OR (95% CI) for glaucoma comparing participants with pre-diabetes to those without diabetes or pre-diabetes was 0.88 (95% CI 0.45 to 1.75). Diabetes duration was also significantly associated with glaucoma. Among participants with diabetes, the multivariable-adjusted OR for glaucoma comparing participants with a duration of disease ≥ 5 years to those with a duration of disease < 5 years was 3.90 (95% CI 1.63 to 9.32).

The prevalence of glaucoma in patients with and without metabolic syndrome was 5.3 and 3.6%, respectively (P = 0.06). The OR for glaucoma comparing participants with to those without metabolic syndrome was 1.30 (95% CI 0.83 to 2.03) in age-, sex-, and race / ethnicity-adjusted models and 1.13 (95% CI 0.60 to 2.16) in fully adjusted models (**Table 3**). In fully adjusted models, none of the individual components of the metabolic syndrome or the presence of insulin resistance were significantly associated with the prevalence of glaucoma (**Table 3**).

In dose-response models with glucose biomarkers modeled as continuous variables or categorized in quartiles, the prevalence of glaucoma increased with increasing biomarker levels but the trends were only statistically significant for fasting glucose (**Table 4**). In fully adjusted models, the OR for glaucoma comparing the fourth to the first quartiles of fasting glucose, insulin, HOMA-IR, and HbA1C were 1.20 (95% CI 0.67 to 2.13; P trend 0.27), 1.22 (95% CI 0.54 to 2.75; P trend 0.75), 1.37 (95% CI 0.57 to 3.27; P trend 0.19) and 1.55 (95% CI 0.59 to 4.08; P trend 0.48), respectively. In spline models, however, the dose-response relationships between markers of glucose metabolism and the prevalence of glaucoma were hockey-stick shaped for insulin, HOMA-IR, and HbA1C and J-shaped for fasting glucose (**Figure 1**). The P

values for the non-linear spline terms in the restricted cubic models were significant for all glucose biomarkers ($p < 0.001$ for all).

DISCUSSION

In a large sample representative of the general US population, the prevalence of glaucoma was higher in participants with diabetes compared to those with no glucose abnormality, even after controlling for multiple potential confounders. Pre-diabetes and the metabolic syndrome and its components were not consistently associated with the prevalence of glaucoma. However, markers of glucose metabolism showed significant non-linear associations with glaucoma prevalence, including hockey-stick shaped associations for fasting insulin, HbA1c and HOMA-IR, and a J-shaped association for fasting glucose. These non-linear relationships suggest threshold effects for the association of glucose metabolism markers and glaucoma.

The association between diabetes and glaucoma has been evaluated in many studies [9,13–15,17,29,30]. An increased risk of glaucoma in persons with diabetes compared to those who did not have diabetes was also observed in the Beaver Dam Eye study, the Blue Mountains Eye study, the Los Angeles Latino Eye Study and several other population-based studies [3,5,16,19,31–35], but some well-known cohorts did not show statistically significant associations [9,14,17]. The discrepancy with these studies may be attributed to study population, sample size, methods to assess diabetes or glaucoma, or drop-out rates. The Baltimore Eye Survey was primarily composed of African Americans and used self-report to define diabetes [9]. The Rotterdam Study used a prospective cohort design, but had few participants with diabetes and a high drop-out rate, so that the results were based only on 5 incident cases of glaucoma among 264 participants with diabetes [14]. The Singapore Malay Eye Study used random serum glucose

measurements instead of fasting glucose to define diabetes, which may result in substantial underdiagnosis, and had also limited power to identify an association beteween diabetes and glaucoma [17]. In spite of these negative studies, the majority of the epidemiological evidence points to an increased prevalence of glaucoma in patients with diabetes.

Few studies have evaluated the association between metabolic syndrome or glucose metabolism biomarkers and glaucoma, with conflicting results [16–19]. In the Singapore Malay Eye Study, participants with metabolic syndrome had a lower prevalence of glaucoma [17], while the number of metabolic syndrome components was positively associated with the hazard of open-angle glaucoma in a US cohort [19]. As for HbA1c and glucose, the Singapore Malay Eye Study showed an elevated but nonsignificant trend while a case-control study in Europe showed a significantly positive association between increased HbA1c levels and glaucoma [16]. In our study, the association between glucose metabolism biomarkers and the prevalence of glaucoma was non-linear and affected only to participants in the higher half of the distribution of glucose metabolism parameters. These findings suggest that a certain degree of impairment in glucose metabolism is needed before glaucoma appears as a complication of insulin resistance.

In addition to the level of glucose metabolism biomarkers, the duration of the metabolic abnormalities may also be important in determining glaucoma risk. We found that duration of diabetes was significantly associated with an increased prevalence of glaucoma, but we did not have information on the duration of the elevations in glucose metabolism biomarkers or on their trajectories over time. Additional research is needed to confirm these thresholds and to understand the increase in glaucoma risk with increasing duration in glucose metabolism abnormalities.

Several biological mechanisms could explain an increased risk of glaucoma in patients with diabetes. Diabetes may induce structural and functional abnormalities to the small blood vessels feeding the optic nerve, resulting in damage to the optic nerve and the retinal nerve fiber layer [36]. Besides the vascular implications, diabetes may also exacerbate glaucomatous optic neuropathy by increasing the susceptibility of retinal ganglion cells to apoptosis due to elevated intraocular pressure (IOP) [37]. This mechanism may also explain progressive optic nerve injury and neuronal damage with a longer duration of diabetes. Furthermore, diabetic retinopathy may also compromise the glial and neuronal elements, impair retinal function and metabolism, and result in accelerated degeneration of retinal inner neurons [38].

The potential mechanisms underlying the association between glucose metabolism abnormalities and the prevalence of glaucoma in subjects without diabetes are unclear. The presence of the metabolic syndrome and elevated levels of glucose, HOMA-IR and glycosylated hemoglobin may be associated with increased levels of IOP, a key causal factor for glaucoma [31,39–44]. Hyperglycemia increased fibronectin production in the bovine trabecular meshwork, which may increase the resistance to aqueous humor outflow and lead to elevated IOP [45]. Moreover, hyperglycemia could induce apoptosis in retinal neuronal cells through the hexosamine biosynthetic pathway [46]. Additionally, hyperglycaemia-induced oxidative stress and advanced glycation end products may increase apoptotic death in retinal neurons [47,48].

Several limitations need to be considered in the interpretation of our findings. First, the cross-sectional nature of this study limited our ability to establish the causality of the observed associations. Second, while we used high quality laboratory methods and fasting plasma samples to assess glucose metabolism status, the prevalence of glaucoma was assessed by self-report without an ophthalmologic exam. Although the prevalence of glaucoma in NHANES

was similar to that reported in other US studies [46], the lack of a clinical assessment of glaucoma may have resulted in underdiagnosis and recall bias. Additional studies with high quality measurements of both glucose metabolism parameters and glaucoma status are needed to confirm our findings. Third, the increased prevalence of glaucoma in patients with diabetes and in those with longer duration of diabetes may have been overestimated because of more frequent ophthalmology visits in persons with compared to those without diabetes. We did not have information on the frequency of eye examinations in study participants, but other studies suggested that this type of surveillance bias could not completely account for the positive association between diabetes and glaucoma risk [5,31]. In the Blue Mountains Eye study, most cases of glaucoma had been diagnosed before the diabetes diagnosis[5], and the Nurses' Health Study also showed that the prospective association between diabetes and glaucoma was unaltered when adjusting for factors related with the number of eye examinations [31]. In spite of these limitations, the large sample size, the standardization and rigorous quality control procedures of NHANES, and the generalizability of the findings to the general US population are important strengths that add to the relevance of our findings.

Glaucoma has a long latency period, in which glaucomatous optic nerve damage is ongoing but remains asymptomatic until later stages. Since vision loss is irreversible, screening and early detection of glaucoma is important in persons with diabetes, given the increased risk for glaucoma and the high frequency coexistence of other mechanisms for vision loss. The adherence to regular ophthalmological exams should be emphasized in diabetic patients, especially among those with long duration of diabetes, regardless of age. Our results also indicate that ophthalmologist referral may be considered for adults without diabetes but with elevated levels of glucose biomarkers.

In conclusion, data from NHANES 2005 – 2008, a large sample representative of the general US population, showed a higher prevalence of glaucoma in patients with diabetes, particularly in those with longer duration of disease, as well as an increased prevalence of glaucoma with increasing levels of glucose metabolism abnormalities in participants in the higher end of the distribution of glucose metabolism parameters. The mechanisms underlying these associations and the impact of the duration of glucose abnormalities on glaucoma risk need to be established in future studies. Our results support the recommendation that patients with diabetes, as well as those with elevated levels of glucose metabolism parameters, undergo regular ophthalmological exams to monitor for the onset or progression of glaucoma.

Table 1. Characteristics of study participants by glaucoma status.*

	Overall N = 3,026	Glaucoma No N = 2,835	Glaucoma Yes N = 191	p-value†
Age, year	57.0 (0.4)	56.5 (0.4)	68.7 (1.5)	< 0.001
Female, %	53.2 (1.2)	53.2 (1.1)	52.3 (4.9)	0.87
Race, %				0.009
Mexican American	5.6 (0.8)	5.7 (0.8)	4.5 (1.6)	
NonHispanic white	76.2 (2.1)	76.4 (2.1)	71.6 (4.8)	
NonHispanic black	10.2 (1.4)	9.8 (1.4)	17.8 (3.7)	
Others	8.0 (1.1)	8.1 (1.1)	6.2 (2.5)	
Education, %				0.005
< High school	18.5 (1.2)	18.0 (1.1)	29.0 (5)	
High school	27.0 (1.3)	26.9 (1.3)	30.6 (5.2)	
> High school	54.5 (2.1)	55.1 (2.1)	40.4 (4.9)	
Waist circumference, cm	100.3 (0.4)	100.2 (0.4)	103 (1.3)	0.04
Systolic blood pressure, mm Hg	126.9 (0.5)	126.4 (0.5)	136.3 (2.2)	< 0.001
Diastolic blood pressure, mm Hg	70.7 (0.4)	70.9 (0.4)	65.7 (1.7)	0.005
Body mass index, kg/m^2	29.0 (0.1)	29.0 (0.1)	29.7 (0.5)	0.15
Insulin, uU/mL ‡	11.2 (0.3)	11.2 (0.3)	11.9 (1.1)	0.54
Serum fasting glucose, mg/dL ‡	103.5 (0.7)	103.4 (0.7)	108.6 (2.0)	0.01
HDL, mg/dL	55.5 (0.3)	55.5 (0.3)	55.4 (1.5)	0.97
Triglycerides, mg/dL	146.0 (2.7)	145.6 (2.7)	154.0 (12.7)	0.52
HbA1c, % ‡	5.5 (0.02)	5.5 (0.02)	5.7 (0.08)	0.01
HOMA-IR ‡	3.0 (0.1)	3.0 (0.1)	3.3 (0.4)	0.40

* Data are means (SEs) or percentages (SEs).
† P value for homogeneity of means or proportions comparing participants with to those without glaucoma.
‡ Values are based on the subsample of participants not taking insulin or medication for diabetes (N = 2,409).

Table 2. Prevalence of glucose metabolism abnormalities by glaucoma status.*

	Overall N = 3,026	Glaucoma		p-value†
		No N = 2,835	Yes N = 191	
Diabetes, %	17.1 (0.9)	16.1 (0.9)	38.8 (4.1)	<0.001
Prediabetes, %	49.0 (1.4)	49.4 (1.4)	40.4 (3.7)	0.34
Insulin resistance, %	43.4 (1.5)	43.1 (1.5)	49.8 (4.7)	0.13
Metabolic syndrome, %	32.1 (1.2)	31.7 (1.2)	41.1 (5.4)	0.06
Elevated waist circumference, %	60.3 (1.4)	60.0 (1.4)	66.4 (4.1)	0.14
Elevated blood pressure, %	42.1 (1.1)	41.1 (1.1)	63.3 (4.1)	<0.001
Elevated triglyceride, %	33.7 (0.9)	33.7 (1.0)	33.6 (5.5)	0.98
Reduced HDL, %	24.0 (0.8)	24.2 (0.8)	18.0 (3.9)	0.17
Elevated fasting glucose, %	28.8 (1.4)	28.2 (1.4)	43.3 (3.7)	<0.001
Duration of diabetes, years	11.7 (0.6)	11.3 (0.6)	15.2 (1.8)	0.04

* Data are percentages or means (SEs).

† P value for homogeneity of means or proportions comparing participants with to those without glaucoma.

Table 3. Odds ratio and 95% CIs for the presence of glaucoma.

	Crude model	Model 1†	Model 2‡
Diabetes			
HbA1c or fasting glucose*	3.99 (2.05, 7.76)	2.09 (1.11, 3.92)	1.80 (0.93, 3.47)
Fasting glucose only§	3.83 (2.24, 6.55)	2.28 (1.37, 3.81)	2.12 (1.23, 3.67)
HbA1c only†	4.52 (2.65, 7.68)	2.65 (1.49, 4.71)	2.10 (1.19, 3.71)
Prediabetes			
HbA1c or fasting glucose*	1.36 (0.72, 2.56)	0.96 (0.52, 1.75)	0.88 (0.45, 1.75)
Fasting glucose only§	1.23 (0.75, 2.02)	1.02 (0.63, 1.66)	1.01 (0.57, 1.82)
HbA1c only†	2.63 (1.53, 4.51)	1.72 (0.98, 3.05)	1.57 (0.85, 2.92)
Metabolic syndrome	1.50 (0.98, 2.29)	1.30 (0.83, 2.03)	1.13 (0.60, 2.16)
Elevated waist circumference	1.31 (0.91, 1.90)	1.19 (0.81, 1.75)	0.89 (0.55, 1.45)
Elevated blood pressure	2.47 (1.71, 3.56)	1.38 (0.97, 1.97)	1.39 (0.92, 2.09)
Elevated triglyceride	0.99 (0.59, 1.68)	1.09 (0.65, 1.81)	0.90 (0.52, 1.57)
Reduced HDL	0.69 (0.40, 1.18)	0.83 (0.47, 1.47)	0.73 (0.35, 1.52)
Elevated fasting glucose	1.95 (1.40, 2.70)	1.35 (1.00, 1.83)	1.29 (0.85, 1.95)
Diabetes duration > 5 years	2.48 (1.06, 5.76)	2.20 (1.02, 4.73)	3.90 (1.63, 9.32)
Insulin resistance ||	1.19 (0.78, 1.81)	1.22 (0.78, 1.90)	1.14 (0.64, 2.01)

†Adjusted for age, gender, and ethnicity.

‡Further adjusted for smoking, physical activity, alcohol intake, education, and BMI.

* Diabetes defined as self-report, HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, or taking diabetic medications. Pre-diabetes defined as self-report, HbA1c ≥5.7% to < 6.5%, or fasting glucose ≥100 mg/dL to <126 mg/dL.

§Diabetes defined as self-report, HbA1c ≥6.5%, or taking diabetic medications. Pre-diabetes defined as self-report or HbA1c ≥5.7% to <6.5%.

† Diabetes defined as self-report, fasting glucose ≥126 mg/dL or taking diabetic medications. Pre-diabetes defined as self-report or fasting glucose ≥100 mg/dL to <126 mg/dL.

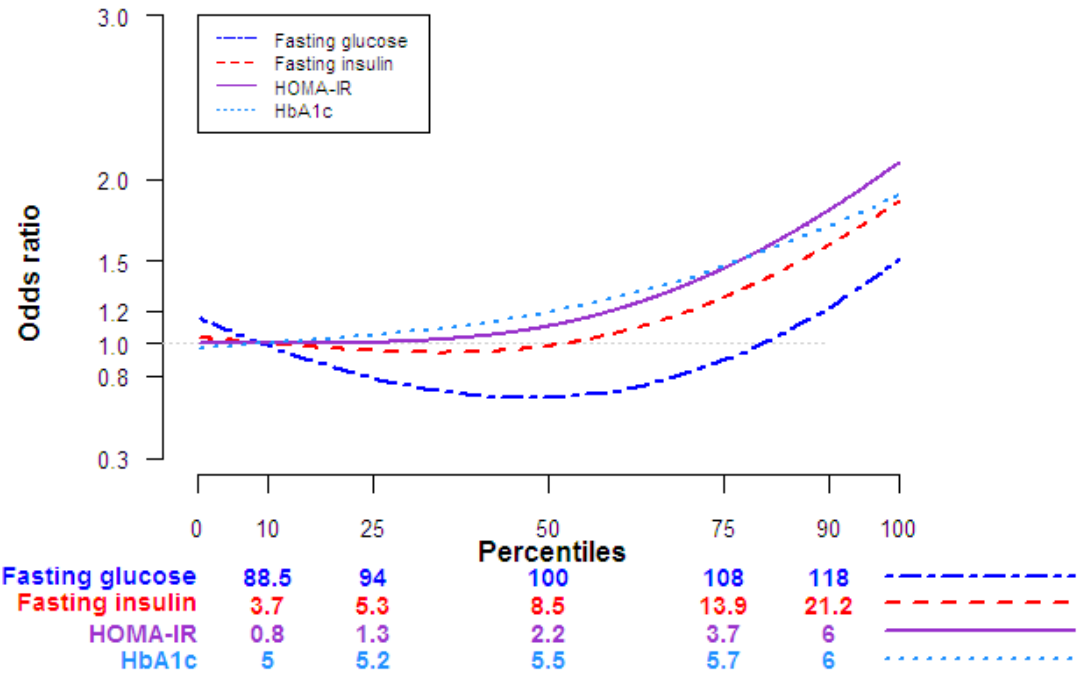
|| Values are based on the subsample of participants not taking insulin or medication for diabetes.

Table 4. Association between markers of glucose metabolism and the presence of glaucoma*

	Odds ratio for glaucoma					P value for quadratic trend
	80^{th} vs. 20^{th}	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Fasting glucose						
Crude Model	1.37 (1.13, 1.64)	1.00 (reference)	0.71 (0.37, 1.34)	1.06 (0.55, 2.06)	1.56 (0.96, 2.56)	0.02
Model 1†	1.22 (0.97, 1.54)	1.00 (reference)	0.67 (0.35, 1.29)	0.98 (0.51, 1.88)	1.05 (0.64, 1.72)	0.47
Model 2‡	1.30 (1.00, 1.68)	1.00 (reference)	0.67 (0.34, 1.34)	1.08 (0.47, 2.47)	1.20 (0.67, 2.13)	0.26
Fasting Insulin						
Crude Model	1.06 (0.65, 1.73)	1.00 (reference)	1.00 (0.55, 1.81)	0.96 (0.44, 2.06)	1.14 (0.61, 2.15)	0.83
Model 1†	1.16 (0.67, 2.01)	1.00 (reference)	1.02 (0.54, 1.90)	0.97 (0.44, 2.11)	1.32 (0.70, 2.49)	0.54
Model 2‡	1.13 (0.53, 2.41)	1.00 (reference)	0.92 (0.43, 1.98)	0.80 (0.30, 2.14)	1.22 (0.54, 2.75)	0.56
HOMA-IR						
Crude Model	1.16 (0.70, 1.92)	1.00 (reference)	0.67 (0.34, 1.35)	1.36 (0.67, 2.76)	1.15 (0.61, 2.17)	0.24
Model 1†	1.21 (0.70, 2.11)	1.00 (reference)	0.68 (0.34, 1.39)	1.39 (0.71, 2.71)	1.22 (0.64, 2.34)	0.17
Model 2‡	1.25 (0.57, 2.72)	1.00 (reference)	0.61 (0.28, 1.34)	1.27 (0.53, 3.05)	1.37 (0.57, 3.27)	0.22
HbA1C						
Crude Model	1.43 (1.16, 1.77)	1.00 (reference)	1.43 (0.62, 3.31)	2.35 (0.95, 5.85)	3.91 (1.75, 8.71)	0.003
Model 1†	1.23 (0.94, 1.60)	1.00 (reference)	1.10 (0.48, 2.51)	1.60 (0.61, 4.21)	1.86 (0.80, 4.28)	0.21
Model 2‡	1.15 (0.85, 1.55)	1.00 (reference)	0.96 (0.38, 2.40)	1.51 (0.53, 4.30)	1.55 (0.59, 4.08)	0.32

* Conducted in people not taking diabetes medications.
† Adjusted for age, gender, and ethnicity.
‡ Further adjusted for smoking, physical activity, alcohol intake, education, and BMI.

Figure 1. Adjusted odds ratio for glaucoma by levels of markers of glucose metabolism.



Adjusted odds ratios were estimated using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of the distribution of each marker of glucose metabolism. The reference value (odds ratio = 1) was set at the 10th percentile of each parameter. Odds ratios were adjusted for age, sex, race, education, smoking status, physical activity, alcohol consumption, and body mass index (see text for details).

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CHAPTER 5

A LONGITUDINAL STUDY OF AGE-RELATED CHANGES IN INTRAOCULAR PRESSURE: THE KANGBUK SAMSUNG HEALTH STUDY

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ABSTRACT

Purpose: To examine the longitudinal association between age and intraocular pressure (IOP) in a large sample of Korean men and women.

Methods: We conducted a prospective cohort study of 274,064 young and middle age Korean adults with normal fundoscopic findings followed from January 1, 2002 to Feb 28, 2010. Health exams were scheduled annually or biennially. At each visit, IOP was measured in both eyes with automated noncontact tonometers. The longitudinal change in IOP with age was evaluated using three-level mixed models for longitudinal paired-eye data accounting for correlations between paired eyes and repeated measurements over time.

Results: In fully adjusted models, the average longitudinal change in IOP per one-year increase in age was -0.065 mm Hg (95% CI -0.068 to -0.063), with marked sex differences ($P < 0.001$). In men, the average annual IOP change was -0.093 mm Hg (95% CI -0.096 to -0.091) throughout follow-up. In women, the average annual IOP change was -0.006 mm Hg (95% CI -0.010 to -0.003), with a relatively flat association in the middle-age range of 30–59 years and more marked annual decreases at younger and older ages.

Conclusions: IOP was inversely associated with age in a large cohort of Korean adults, and this association was stronger in men compared with women. Further research is needed to better understand the underlying mechanisms and to reconsider cutoffs for defining high IOP by age and sex groups in Asian populations.

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INTRODUCTION

Elevated intraocular pressure (IOP) is a major risk factor for the development of primary open-angle glaucoma,[1] and even in normal tension glaucoma the reduction of IOP may slow the progression of visual field loss.[2] Population based studies of prevalence and incidence of glaucoma consistently show a steady increase with age.[3-9] Consistent with this finding, cross-sectional and longitudinal studies have shown that IOP increases with age in Western populations. [2, 10-14]

In the 1980s, Shiose and Kawase reported an inverse association between age and IOP in a Japanese population,[15, 16] and suggested that these results reflect ethnic differences or environmental effects. Several cross-sectional studies have confirmed these findings in Japanese[17, 18] and in other East Asian populations,[19-21] but the only two longitudinal prospective studies have been inconsistent. Nomura et al.[22] reported that IOP significantly increased with age in Japanese men and women, while Nakano et al.[23] reported that IOP decreased with age in young and middle-aged Japanese men. The inconsistencies of these two studies could be because of the difference in study populations. Nomura et al. examined the association in 69,643 Japanese office workers and their family members, while Nakano et al. selected participants from 2,987 Japanese male aircraft crew members. They also may be due to the methodological issues related to the analysis of the longitudinal IOP trajectories as Nomura et al. used a mixed effects model for longitudinal analysis, while Nakano et al. individually calculated coefficients for 11 measurement points using linear regression.

Since cross-sectional studies do not provide estimates of within-subject IOP trajectories, we conducted a longitudinal cohort study to evaluate the influence of age on IOP in a large sample of healthy Korean men and women attending regular health screening visits.

METHODS

Study design and population

The Kangbuk Samsung Health Study is a longitudinal cohort study of 281,238 adult Korean men and women who underwent comprehensive screening health examinations at the two Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea, from January 1, 2002, to February 28, 2010. Over 80% of the participants were employees of various companies or local government organizations and their spouses, who took employer-paid annual or biennial health screening exams required by the Korean Industrial Safety and Health Law. The remaining participants voluntarily purchased screening exams at the health exam center.

The present analysis included 280,911 study participants with valid IOP readings in at least one screening visit between January 1, 2002 and February 28, 2010 (the total number of visits was 604,416). We excluded 9,225 visits after participants developed an absolute difference in IOP between both eyes greater than 6 mm Hg, as this is a marker of high risk of glaucoma;[24] 1,652 visits with missing fundus photograph; 15,458 visits after participants developed abnormal findings in fundus photographs; and 100 visits for participants with missing IOP measurements at all visits . Thus, the final sample included 274,064 participants (119,723 women and 154,341 men) free of eye disease with a total of 577,981 screening visits.

This study was approved by the Institutional Ethics Committee of the Kangbuk Samsung Hospital. The Ethics Committee waived the requirement of informed consent as we only used de-identified data routinely collected during health screening visits.

Measurements

Health exams were scheduled every 2 years for participants younger than 40 years of age and every year for participants 40 years of age or older. At each visit, IOP was measured in both eyes with automated noncontact tonometers (2002–2004: TX-10, Canon, Tokyo, Japan; 2005–2008: TX-F, Topcon, Itabashi, Tokyo, Japan; 2009 onwards: CT-80, Topcon, Itabashi, Tokyo, Japan). Extreme IOP readings below 5 mm Hg (0.02%) or above 30 mm Hg (0.16%) were discarded because of the potential for measurement error. The time of registration at the exam center was within two hours of IOP measurement and hence used as the approximate IOP measurement time (classified into morning or afternoon). Fundus photographs were taken with a nonmydriatic fundus camera (CR6-45NM, Canon, Tokyo, Japan).

Demographic characteristics, smoking status, alcohol consumption, physical activity, medical history, and medication use were collected by a standardized self-administered questionnaire. Smoking status was categorized into never, former, or current smoking, frequency of current alcohol consumption was categorized into < 1, 1–3, or > 3 days/week, and frequency of vigorous physical activity was categorized into none, 1–3, or > 3 times/week. Height and weight were measured with the participants wearing a lightweight hospital gown and no shoes. Body mass index was calculated as weight in kilograms divided by height in meters squared. Sitting blood pressure and heart rate were measured by trained nurses. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, a self-reported history of hypertension, or current use of antihypertensive medications.

Serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured in fasting blood samples collected after at least 12 hours of fasting. Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dL, a self-reported history

of diabetes, or current use of antidiabetic medications. Dyslipidemia was defined as total cholesterol $\geq$ 240 mg/dL, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women, serum triglycerides $\geq$ 150 mg/dL, report of a previous diagnosis, or current use of lipid lowering medications.

Statistical analysis

The primary objective of this study was to assess the longitudinal change in IOP with age. To account for correlations in IOP measurements arising from both paired eyes and repeated measurements over time in the same participant, the main analyses consisted of three-level linear mixed models for longitudinal paired-eye data.[25, 26] Details of the models are provided in the **Statistical Appendix**. Briefly, we modeled linear trajectories in IOP with age for each eye at the first level, variations in IOP trajectories between both eyes of the same participant at the second level, and variations in IOP trajectories across participants at the third level. These mixed models provided the average longitudinal change in IOP per one-year increase in age, while they allowed for random variations in longitudinal changes among participants and between eyes within participants according to normal distributions with unstructured variance-covariance matrices. For comparison with previous studies, we also evaluated the cross-sectional association between age and IOP by using random-intercept linear models for paired-eye data from the baseline visit, which estimated the average cross-sectional difference in baseline IOP per one-year increase in baseline age. Details of cross-sectional analyses are also provided in the **Statistical Appendix**.

To adjust for confounding and to evaluate potential mediating factors, we used three models with increasing degrees of adjustment. The first model was crude. The second model adjusted for sex, study center (Seoul or Suwon), and height (continuous) as time-constant

covariates, as well as for IOP measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), and physical activity (none, 1–3, or > 3 times/week) as time-varying covariates. The third model further included potential mediators of the effect of age as time-varying covariates, including heart rate (continuous), body mass index (continuous), hypertension (no or yes), diabetes (no or yes), and dyslipidemia (no or yes).

We accommodated distinct linear IOP trajectories in age intervals < 30, 30–39, 40–49, 50–59, and ≥ 60 years by extending the above mixed models with fixed-effects linear spline terms for age at follow-up with knots at 30, 40, 50, and 60 years.[27] Smooth longitudinal trends in IOP with age were also obtained by adding fixed-effects restricted quadratic spline terms for age with the same knots described above. To evaluate potential heterogeneity of IOP trajectories by sex, interactions of sex and age were included as fixed effects in the corresponding mixed models. We conducted sensitivity analyses without excluding participants with abnormal fundoscopy findings or with between-eye differences in IOP greater than 6 mmHg (280,911 participants with 604,416 visits). In addition, we performed a sensitivity analysis restricted to participants with two or more screening visits (130,991 participants with 435,262 visits). All reported *P* values were two-sided and the significance level was set at 0.05. Statistical analyses were undertaken using Stata (version 12; Stata Corp., College Station, Texas).

RESULTS

The mean (SD) age and IOP of study participants at baseline were 40.2 (9.9) years and 13.6 (2.5) mm Hg, respectively (**Table 1**). Overall, women had lower mean baseline IOP levels than men, although the difference in baseline IOP levels between sexes decreased among

participants older than 50 years of age. Compared with men, women were less likely to smoke, drink alcohol, and exercise, and to have hypertension, diabetes, and dyslipidemia at baseline. Women had also lower mean baseline body mass index and higher heart rate. Participants with two or more screening visits (n = 133,651) were generally younger, more educated, healthier, less likely to have diabetes, hypertension or dyslipidemia, and more likely to have a higher IOP compared with participants with only a single screening visit.

In longitudinal analyses, age showed a significant inverse association with IOP (**Table 2**). In fully adjusted models, the average longitudinal decrease in IOP for each one-year increase in age was -0.065 mm Hg (95% confidence interval [CI] -0.068 to -0.063 mm Hg). The longitudinal downward trend in IOP with increasing age, however, was markedly different between sexes and across age intervals (all *P* values < 0.001). For men, the average annual IOP change was -0.093 mm Hg (95% CI -0.096 to -0.091 mm Hg) over the entire age range and it varied from -0.142 to -0.080 mm Hg across the different age intervals. For women, the average annual IOP change was -0.006 mm Hg (95% CI -0.010 to -0.003 mm Hg) over the entire age-range, with a relatively flat association between 30–59 years of age and more marked annual decreases of -0.167 and -0.076 mm Hg at younger and older ages, respectively. The longitudinal decrease in IOP with age and the differences between sexes were also evident in restricted quadratic spline models, which confirmed the homogeneous linear decline in men and the weaker nonlinear association in women (**Figure 1**). Sensitivity analyses restricting the study population to participants with at least two screening visits did not materially affect the result. Additional analyses without excluding participants with abnormal fundoscopy findings or with between-eye differences in IOP greater than 6 mmHg also yielded similar results (data not shown).

For comparison with previous studies, we also estimated the cross-sectional association between age and IOP at baseline. In cross-sectional analyses, age was also significantly inversely associated with IOP, although this baseline association was weaker than the longitudinal relationship (**Supplementary Table 1** and **Supplementary Figure 1**). The average cross-sectional differences in baseline IOP per one-year increase in baseline age were -0.023 mm Hg (95% CI -0.024 to -0.022 mm Hg) overall, -0.036 mm Hg (95% CI -0.037 to -0.034 mm Hg) in men, and -0.008 mm Hg (95% CI -0.010 to -0.007 mm Hg) in women.

DISCUSSION

In this large cohort of Korean adults, IOP decreased with age but the decline was stronger in men compared with women and in participants <30 years of age compared with older participants. Cross-sectional associations between age and IOP followed a similar pattern, but underestimated the magnitude of the longitudinal association. The large sample size, the wide age range, the availability of repeated IOP measurements in both eyes in study participants, and the use of longitudinal analyses that consider the trajectories of individual eyes in each participant add to the strength of our findings.

The inverse longitudinal and cross-sectional associations between age and IOP in our study are compatible with other cross-sectional[16-19, 21, 28, 29] and longitudinal studies[23] conducted in Asian populations with the exception of a longitudinal study in Japan.[22] On the contrary, most cross-sectional[2, 10, 30-33] and longitudinal studies[34-36] in Western populations showed a positive association between age and IOP, although some studies showed no[11, 37, 38] or inverse associations.[39, 40] Aging is associated both with reduced production of aqueous humor,[41] which leads to a reduction of IOP, and with structural changes in the trabecular meshwork, which increase the resistance to aqueous humor outflow, increasing IOP.[42] The net change in IOP may

be determined by the balance between these processes, which may differ in Western and Asian populations.

The mechanisms for the differences in the association between age and IOP between Western and Asian populations are unclear. Lifestyle factors and environmental exposures have been proposed,[22, 29, 35] but no single responsible factor has been clearly identified. Anatomical eye features linked to IOP (iris color, central corneal thickness, anterior chamber depth, etc.) could have different effects in Asian compared with Western subjects,[23, 31, 39] but additional research is needed to understand the role of anatomical eye differences in IOP trajectories. Finally, the decrease in IOP with age in Asian populations has been ascribed to methodological factors such as selection bias due to non-participation in cross-sectional studies or drop out in longitudinal studies of elderly subjects with higher IOP and had higher comorbidities,[22] or to cohort effects with younger individuals adopting Western lifestyles. In our study, however, we observed inverse associations between age and IOP even among participants <30 years of age, who are unlikely to be subject to selection bias due to major comorbidities. In addition the decrease in IOP with advancing age was observed across all age groups in the longitudinal analyses, with no clear cohort effects.

Sex-related differences in the distribution of IOP and its changes with age have also been inconsistent across studies. In our study, women had a lower IOP compared with men, a pattern also reported in the the Egna-Neumarkt[2] and the Gutenberg Health[39] studies. In contrast, in the Barbados Eye study,[30] the Rotterdam study[43], the Los Angeles Latino Eye Study[44] and the Beaver Dam Eye Study,[11] men had lower IOP, while the Framingham Eye study[33] and the Health and Nutrition Examination Survey[45] reported no association between sex and IOP. It has been hypothesized that the higher IOP in men could be due to a higher prevalence of

cardiovascular risk factors in men.[39, 44] However, adjusting for cardiovascular risk factors in our study did not materially change the association of IOP with age and sex.

Hormonal differences and the effect of menopause may also explain some gender differences in IOP.[46] Estrogen may affect the inflow of aqueous humour, the ciliary body and the trabecular meshwork.[47] Indeed, an Indian study showed that the IOP in postmenopausal was higher compared with premenopausal women, and attributed this difference to the higher levels of testosterone and the decrease in estrogen and progesterone levels with the onset of menopause.[48] Use of hormone replacement therapy has also been associated with a lower IOP.[49, 50] Further research is needed to understand gender-related differences in IOP.

Our study has several strengths. The Kangbuk Samsung Health Study is by far the largest population-based cohort study evaluating the association between age and IOP. The longitudinal nature allowed us to evaluate within-person trajectories in IOP, avoiding many biases in cross-sectional studies. The drop-out rate was modest (over 77% of participants recruited in the first year of the study had at least one additional follow-up visit), and we were able to incorporate multiple potential confounders and intermediate factors. Finally, we used a statistical approach based on a three-level hierarchical approach to appropriately account for correlations between eyes and between visits for each participant.

Some limitations of our study also need to be considered. First, we used non-contact tonometers to measure IOP instead of applanation tonometers, considered the gold standard. This may have resulted in measurement error that may have underestimated study associations. Second, our study included preferentially young and middle-age adults, and only 6% of study participants had 60 years of age or over at baseline. Additional studies with follow-up of older participants are needed to better understand the relationship of age with IOP beyond the 6th

decade of age in Asian populations. Finally, our study population consisted of middle-age Korean men and women attending health screening visits, which may limit the generalizability of our findings to other populations.

In conclusion, we found that IOP was inversely associated with age in a large cohort of Korean adults attending health screening visits, an association that was stronger in men compared with women. Further research is needed to better understand the underlying mechanisms and to reconsider cutoffs for defining high IOP by age and sex groups in Asian populations.

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Table 1. Participants' characteristics at baseline.*

Characteristic	Overall	Female	Male	P value†
Participants	274,064	119,723 (43.7)	154,341 (56.3)	
Age, years	40.2 (9.9)	40.5 (10.3)	39.8 (9.5)	< 0.001
Study center				< 0.001
Seoul	184,957 (67.5)	81,423 (68.0)	103,534 (67.1)	
Suwon	89,107 (32.5)	38,300 (32.0)	50,807 (32.9)	
Height, cm	166.2 (8.5)	159.1 (5.5)	171.8 (5.9)	< 0.001
Smoking status				< 0.001
Never	147,039 (54.6)	105,391 (90.8)	41,648 (27.2)	
Former	45,506 (16.9)	4,147 (3.6)	41,359 (27.0)	
Current	76,582 (28.5)	6,497 (5.6)	70,085 (45.8)	
Alcohol drinking, days/week				< 0.001
< 1	172,819 (64.0)	101,902 (86.8)	70,917 (46.4)	
1–3	71,097 (26.3)	12,732 (10.8)	58,365 (38.2)	
> 3	26,319 (9.7)	2,824 (2.4)	23,495 (15.4)	
Physical activity, times/week				< 0.001
0	147,688 (54.6)	74,984 (63.5)	72,704 (47.6)	
1–3	77,994 (28.8)	23,647 (20.0)	54,347 (35.6)	
> 3	45,005 (16.6)	19,427 (16.5)	25,578 (16.8)	
Heart rate, beats/min	67.2 (9.3)	68.3 (9.2)	66.4 (9.3)	< 0.001
Body mass index, kg/m2	23.5 (3.1)	22.4 (3.1)	24.4 (2.9)	< 0.001
Hypertension	47,671 (17.4)	14,501 (12.1)	33,170 (21.5)	< 0.001
Diabetes	10,763 (3.9)	3,416 (2.9)	7,347 (4.8)	< 0.001
Dyslipidemia	115,731 (42.2)	41,852 (35.0)	73,879 (47.9)	< 0.001
Intraocular pressure‡, mm Hg	13.58 (2.66)	13.10 (2.65)	13.95 (2.61)	< 0.001
< 30 years	13.55 (2.71)	13.10 (2.71)	13.99 (2.64)	< 0.001
30–39 years	13.58 (2.70)	12.94 (2.66)	14.05 (2.64)	< 0.001
40–49 years	13.62 (2.60)	13.13 (2.58)	13.97 (2.55)	< 0.001
50–59 years	13.59 (2.57)	13.52 (2.63)	13.66 (2.51)	< 0.001
≥ 60 years	13.34 (2.62)	13.37 (2.67)	13.30 (2.57)	0.13

* Data are means (SDs) or number (%).
† *P* value for homogeneity of means or proportions comparing males and females.
‡ Means (between-subject SDs) for the average intraocular pressure of left and right eyes overall and by age group at baseline.

Table 2. Longitudinal changes in intraocular pressure per 1-year increase in age, overall and by age interval.*

		Age interval, years					
	Overall	**< 30**	**30–39**	**40–49**	**50–59**	**≥ 60**	***P* value†**
No. of subjects/visits							
Overall	274,064 / 577,785	23,021 / 26,033	147,849 / 268,588	92,650 / 204,678	36,318 / 56,144	16,583 / 22,342	
Female	119,723 / 224,085	11,282 / 13,073	61,806 / 105,754	36,796 / 71,273	17,292 / 23,717	8,106 / 10,268	
Male	154,341 / 353,700	11,739 / 12,960	86,043 / 162,834	55,854 / 133,405	19,026 / 32,427	8,477 / 12,074	
Model 1§, mm Hg/year							
Overall	-0.058 (-0.060 to -0.056)	-0.128 (-0.141 to -0.115)	-0.043 (-0.046 to -0.041)	-0.073 (-0.076 to -0.069)	-0.065 (-0.071 to -0.060)	-0.104 (-0.112 to -0.095)	< 0.001
Female	0.000 (-0.003 to 0.004)	-0.160 (-0.177 to -0.144)	0.005 (0.001 to 0.010)	0.004 (-0.001 to 0.009)	0.009 (0.000 to 0.017)	-0.060 (-0.073 to -0.048)	< 0.001
Male	-0.088 (-0.091 to -0.086)	-0.118 (-0.138 to -0.098)	-0.070 (-0.074 to -0.067)	-0.105 (-0.109 to -0.101)	-0.103 (-0.110 to -0.096)	-0.124 (-0.135 to -0.112)	< 0.001
P value‡	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Model 2‖, mm Hg/year							
Overall	-0.059 (-0.061 to -0.057)	-0.161 (-0.173 to -0.148)	-0.046 (-0.049 to -0.043)	-0.070 (-0.073 to -0.067)	-0.061 (-0.067 to -0.056)	-0.108 (-0.117 to -0.099)	< 0.001
Female	0.001 (-0.003 to 0.005)	-0.170 (-0.186 to -0.153)	0.007 (0.002 to 0.011)	0.006 (0.001 to 0.012)	0.007 (-0.001 to 0.016)	-0.065 (-0.079 to -0.052)	< 0.001
Male	-0.087 (-0.090 to -0.085)	-0.127 (-0.148 to -0.107)	-0.071 (-0.074 to -0.067)	-0.103 (-0.106 to -0.099)	-0.103 (-0.110 to -0.095)	-0.120 (-0.132 to -0.109)	< 0.001
P value‡	< 0.001	0.002	< 0.001	< 0.001	< 0.001	< 0.001	
Model 3¶, mm Hg/year							
Overall	-0.065 (-0.068 to -0.063)	-0.166 (-0.179 to -0.154)	-0.054 (-0.056 to -0.051)	-0.074 (-0.077 to -0.071)	-0.073 (-0.078 to -0.067)	-0.112 (-0.121 to -0.103)	< 0.001
Female	-0.006 (-0.010 to -0.003)	-0.167 (-0.184 to -0.151)	0.001 (-0.004 to 0.005)	-0.001 (-0.007 to 0.004)	-0.012 (-0.021 to -0.004)	-0.076 (-0.089 to -0.063)	< 0.001
Male	-0.093 (-0.096 to -0.091)	-0.142 (-0.162 to -0.122)	-0.080 (-0.083 to -0.076)	-0.105 (-0.109 to -0.101)	-0.108 (-0.115 to -0.101)	-0.121 (-0.133 to -0.110)	< 0.001
P value‡	< 0.001	0.06	< 0.001	< 0.001	< 0.001	< 0.001	

* The average longitudinal changes in intraocular pressure per one-year increase in age and their 95% confidence intervals were obtained from linear mixed models with different intersecting linear trends in each age interval, interactions between linear age trends and sex, and random variations in linear age trends among participants and between eyes within participants.

† *P* value for homogeneity of annual changes across all age intervals.

‡ *P* value for homogeneity of annual changes comparing males and females.

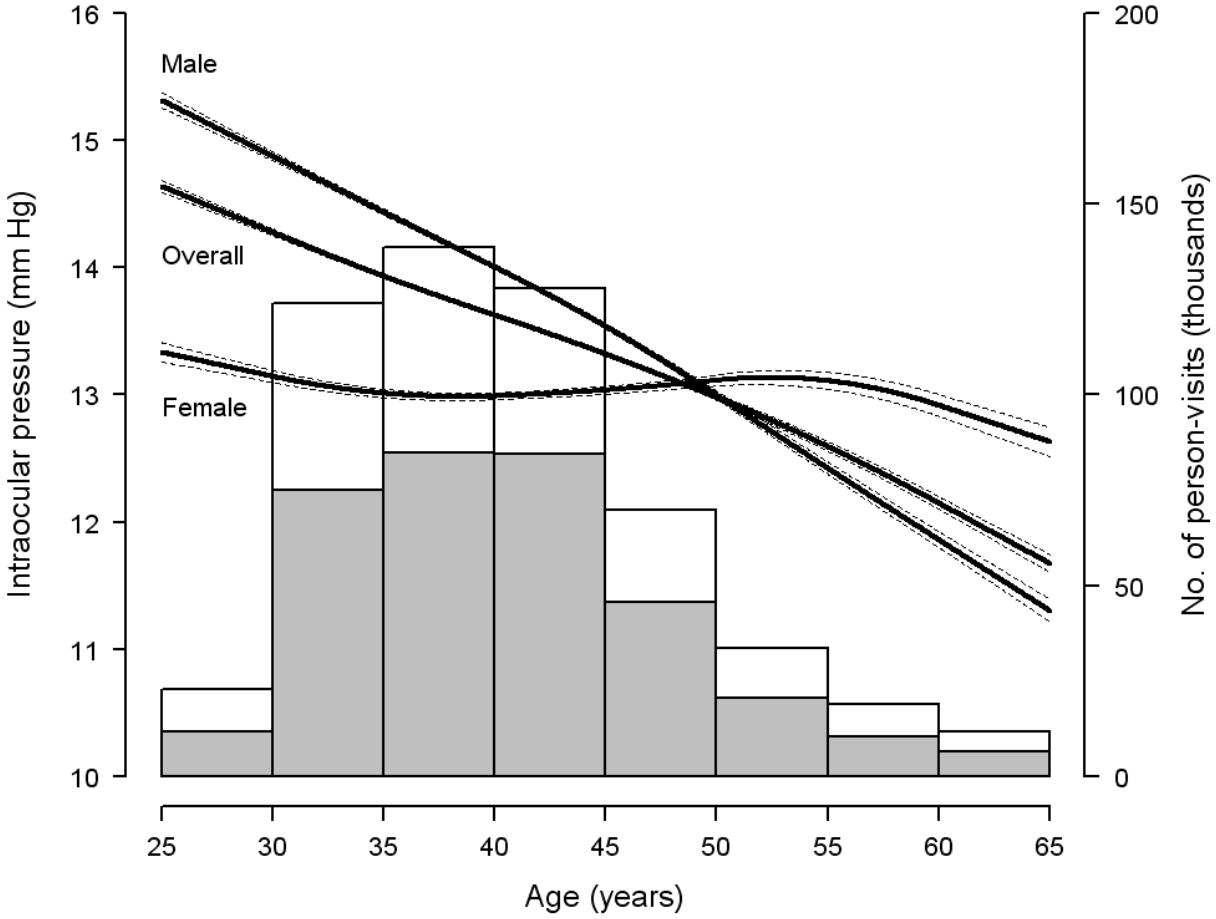
§ Unadjusted.

‖ Adjusted for study center (Seoul or Suwon), height (continuous), and time-varying changes in intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), and physical activity (none, 1–3, or > 3 times/week).

¶ Further adjusted for time-varying changes in heart rate (continuous), body mass index (continuous), hypertension (no or yes), diabetes (no or yes), and dyslipidemia (no or yes).

FIGURE LEGENDS

Figure 1. Longitudinal trend in intraocular pressure by age at follow-up.



Curves represent adjusted average intraocular pressures (solid lines) and their 95% confidence intervals (dashed lines) based on restricted quadratic splines with knots at 30, 40, 50, and 60 years of age. Results were obtained from linear mixed models with interactions between spline terms and sex, random variations in age trends among participants and between eyes within participants, and adjusted for study center (Seoul or Suwon), height (continuous), and time-varying changes in intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), body mass index (continuous), hypertension (no or yes), diabetes (no or yes), and dyslipidemia (no or yes). The histogram represents the age distribution of person-visits among males (shaded bars) and females (white bars).

Supplemental Table 1. Cross-sectional changes in intraocular pressure per 1-year increase in age, overall and by age interval.*

		Baseline age group, years					
	Overall	**< 30**	**30–39**	**40–49**	**50–59**	**≥ 60**	***P* value†**
No. of subjects							
Overall	274,064	23,024	139,881	66,538	29,526	15,095	
Female	119,723	11,283	58,589	27,428	15,002	7,421	
Male	154,341	11,741	81,292	39,110	14,524	7,674	
Model 1§, mm Hg/year							
Overall	-0.004 (-0.005 to -0.003)	-0.045 (-0.058 to -0.033)	0.011 (0.008 to 0.015)	-0.006 (-0.010 to -0.002)	-0.001 (-0.007 to 0.005)	-0.045 (-0.053 to -0.037)	< 0.001
Female	0.016 (0.014 to 0.017)	-0.132 (-0.147 to -0.116)	0.019 (0.014 to 0.025)	0.031 (0.024 to 0.037)	0.030 (0.021 to 0.038)	-0.047 (-0.059 to -0.035)	< 0.001
Male	-0.019 (-0.020 to -0.017)	-0.027 (-0.046 to -0.008)	0.004 (-0.001 to 0.008)	-0.027 (-0.033 to -0.021)	-0.028 (-0.036 to -0.020)	-0.044 (-0.056 to -0.033)	< 0.001
P value‡	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.75	
Model 2‖, mm Hg/year							
Overall	-0.008 (-0.009 to -0.007)	-0.093 (-0.105 to -0.081)	0.007 (0.003 to 0.011)	-0.006 (-0.010 to -0.001)	-0.004 (-0.011 to 0.002)	-0.057 (-0.065 to -0.048)	< 0.001
Female	0.010 (0.009 to 0.012)	-0.146 (-0.162 to -0.130)	0.019 (0.014 to 0.025)	0.024 (0.018 to 0.031)	0.023 (0.014 to 0.033)	-0.057 (-0.070 to -0.044)	< 0.001
Male	-0.026 (-0.027 to -0.024)	-0.042 (-0.061 to -0.023)	-0.002 (-0.007 to 0.002)	-0.032 (-0.038 to -0.026)	-0.036 (-0.045 to -0.027)	-0.048 (-0.060 to -0.037)	< 0.001
P value‡	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.33	
Model 3¶, mm Hg/year							
Overall	-0.023 (-0.024 to -0.022)	-0.111 (-0.122 to -0.099)	-0.005 (-0.009 to -0.002)	-0.020 (-0.024 to -0.015)	-0.025 (-0.031 to -0.019)	-0.065 (-0.073 to -0.056)	< 0.001
Female	-0.008 (-0.010 to -0.007)	-0.158 (-0.173 to -0.142)	0.008 (0.002 to 0.013)	0.006 (-0.001 to 0.013)	-0.005 (-0.014 to 0.004)	-0.074 (-0.086 to -0.062)	< 0.001
Male	-0.036 (-0.037 to -0.034)	-0.061 (-0.080 to -0.042)	-0.013 (-0.018 to -0.009)	-0.041 (-0.047 to -0.035)	-0.048 (-0.056 to -0.039)	-0.052 (-0.064 to -0.041)	< 0.001
P value‡	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.01	

* The average cross-sectional differences in baseline intraocular pressure per one-year increase in baseline age and their 95% confidence intervals were obtained from random-intercept linear models for baseline paired-eye data with different intersecting linear trends in each baseline age group and interactions between linear age trends and sex.
† *P* value for homogeneity of age slopes across all baseline age groups.
‡ *P* value for homogeneity of age slopes comparing males and females.
§ Unadjusted.
‖ Adjusted for study center (Seoul or Suwon), height (continuous), and baseline levels of intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), and physical activity (none, 1–3, or > 3 times/week).
¶ Further adjusted for baseline levels of heart rate (continuous), body mass index (continuous), hypertension (no or yes), diabetes (no or yes), and dyslipidemia (no or yes).

STATISTICAL APPENDIX

Cross-sectional association of intraocular pressure with age at baseline

The cross-sectional association between intraocular pressure (IOP) and age was evaluated by using random-intercept linear models for paired-eye data from the baseline visit.[1] More specifically, the IOP Y_{0ji} at baseline visit $t = 0$ was allowed to vary randomly between eyes $j = 1, 2$ of each participant $i = 1,\ldots, n_0$,

$$Y_{0ji} = \alpha_{0i} + \varepsilon_{0ji},$$

where α_{0i} was the expected baseline IOP for participant i and ε_{0ji} was the between-eye variation in baseline IOP for that participant, which was assumed to be normally distributed with mean 0 and constant variance σ^2. The subject-specific baseline IOP α_{0i} was related to baseline age a_{0i} and other baseline $\mathbf{x}_{0i}$ and time-constant covariates $\mathbf{z}_i$, including sex (male or female), study center (Seoul or Suwon), height (continuous), IOP measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), body mass index (continuous), hypertension (no or yes), diabetes (no or yes), and dyslipidemia (no or yes), through the linear model

$$\alpha_{0i} = \beta_{00} + \beta_{01}(a_{0i} - \bar{a}_0) + \boldsymbol{\beta}'_{02}(\mathbf{x}_{0i} - \bar{\mathbf{x}}_0) + \boldsymbol{\beta}'_{03}(\mathbf{z}_i - \bar{\mathbf{z}}) + b_{0i},$$

where the between-subject variation b_{0i} was assumed to be normally distributed with mean 0 and constant variance τ^2. Combining both models yielded the random-intercept linear model

$$Y_{0ji} = (\beta_{00} + b_{0i}) + \beta_{01}(a_{0i} - \bar{a}_0) + \boldsymbol{\beta}'_{02}(\mathbf{x}_{0i} - \bar{\mathbf{x}}_0) + \boldsymbol{\beta}'_{03}(\mathbf{z}_i - \bar{\mathbf{z}}) + \varepsilon_{0ji},$$

in which the fixed effect β_{00} represented the average baseline IOP at mean baseline values of age $\bar{a}_0$ and covariates $\bar{\mathbf{x}}_0$ and $\bar{\mathbf{z}}$, the fixed effect β_{01} corresponded to the covariate-adjusted average change in baseline IOP per one-year increase in baseline age, and the random effect b_{0i} was the unexplained between-subject variation in baseline IOP.

To allow for nonlinear cross-sectional associations between IOP and age, the above random-intercept model was separately extended with fixed-effects linear spline terms and restricted quadratic spline terms for baseline ages a_{0i} with knots at 30, 40, 50, and 60 years and constrained to be 0 at the mean baseline age $\bar{a}_0$.[2] Also, to evaluate potential heterogeneity of cross-sectional associations by sex, interactions of sex with the homogeneous linear term $a_{0i} - \bar{a}_0$, linear spline terms, and restricted quadratic spline terms were included as fixed effects in the corresponding random-intercept models.

Longitudinal association of intraocular pressure with age

To assess the longitudinal association of IOP with age, we developed linear mixed models for longitudinal paired-eye data using a three-level hierarchical approach.[1] At the first within-eye level, the IOP Y_{tji} at visit $t = 0,\ldots, m_i$ for eye $j = 1, 2$ of participant $i = 1,\ldots, n_0$ was related to age a_{ti} and other subject-specific time-varying covariates $\mathbf{x}_{ti}$ at that visit through the linear model

$$Y_{tji} = \alpha_{0ji} + \alpha_{1ji}(a_{ti} - \bar{a}) + \boldsymbol{\alpha}'_{2ji}(\mathbf{x}_{ti} - \bar{\mathbf{x}}) + \varepsilon_{tji},$$

where α_{0ji} was the expected IOP for eye j of participant i at the overall mean values of age $\bar{a}$ and time-varying covariates $\bar{\mathbf{x}}$, α_{1ji} and $\boldsymbol{\alpha}_{2ji}$ were the expected longitudinal slopes in IOP for that eye associated with age and time-varying covariates, including IOP measurement

time, smoking status, alcohol drinking, physical activity, heart rate, body mass index, hypertension, diabetes, and dyslipidemia, and the within-eye errors ε_{tji} were assumed to be independent and normally distributed with mean 0 and constant variance σ^2.

The second level represented the variation in coefficients α_{0ji}, α_{1ji}, and $\boldsymbol{\alpha}_{2ji}$ between eyes of the same participant. The eye-specific IOP at the overall mean covariates α_{0ji} was allowed to vary randomly between each participant's eyes, whereas the longitudinal slopes in IOP for age α_{1ji} and the other time-varying covariates $\boldsymbol{\alpha}_{2ji}$ were assumed to be fixed for both eyes. Thus, the second-level model was

$$\alpha_{0ji} = \gamma_{00i} + b_{0ji},$$

$$\alpha_{1ji} = \gamma_{10i},$$

$$\boldsymbol{\alpha}_{2ji} = \boldsymbol{\gamma}_{20i},$$

where the between-eye variations within a subject b_{0ji} were assumed to be normally distributed with mean 0 and constant variance τ^2. The longitudinal age slopes α_{1ji} were specified as fixed at eye level because preliminary analyses showed virtually null random variation in longitudinal age slopes between each participant's eyes.

Finally, the third level described the variation in parameters γ_{00i}, γ_{10i}, and $\boldsymbol{\gamma}_{20i}$ across participants. The subject-specific IOP at the overall mean covariates γ_{00i} was linearly related to each participant's mean values of age $\bar{a}_i$ and time-varying covariates $\bar{\mathbf{x}}_i$, as well as to other time-constant covariates $\mathbf{z}_i$, including sex, study center, and height. The subject-specific longitudinal age slopes in IOP γ_{10i} were allowed to vary randomly across participants, while the longitudinal slopes for the other time-varying covariates $\boldsymbol{\gamma}_{20i}$ were assumed to be constant for all participants. Specifically, the third-level model was

$$\gamma_{00i} = \beta_{000} + \beta_{001}(\bar{a}_i - \bar{a}) + \boldsymbol{\beta}'_{002}(\bar{\mathbf{x}}_i - \bar{\mathbf{x}}) + \boldsymbol{\beta}'_{003}(\mathbf{z}_i - \bar{\mathbf{z}}) + b_{00i},$$

$$\gamma_{10i} = \beta_{100} + b_{10i},$$

$$\boldsymbol{\gamma}_{20i} = \boldsymbol{\beta}_{200},$$

where the between-subject variations b_{00i} and b_{10i} were assumed to follow a bivariate normal distribution with mean **0** and constant variance-covariance matrix **V**. Combining the three nested models, we obtained the linear mixed model

$$Y_{tji} = (\beta_{000} + b_{00i} + b_{0ji}) + \beta_{001}(\bar{a}_i - \bar{a}) + \boldsymbol{\beta}'_{002}(\bar{\mathbf{x}}_i - \bar{\mathbf{x}}) + \boldsymbol{\beta}'_{003}(\mathbf{z}_i - \bar{\mathbf{z}})$$

$$+ (\beta_{100} + b_{10i})(a_{ti} - \bar{a}) + \boldsymbol{\beta}'_{200}(\mathbf{x}_{ti} - \bar{\mathbf{x}}) + \varepsilon_{tji}.$$

This mixed model included two nested random effects for the intercept, as well as a random effect for the longitudinal age slope at subject level, to account for correlations arising from both paired-eye data and repeated measurements over time.[3] In particular, the fixed effect β_{000} represented the average IOP at the reference (overall mean) age for a subject with mean covariates, and the random effects b_{00i} and b_{0ji} were the unexplained variations in IOP at the reference age among participants and between eyes within participants, respectively. The fixed effect β_{100} corresponded to the average longitudinal change in IOP per one-year increase in age adjusted for time-varying covariates and the random effect b_{10i} was the unexplained between-subject variation in longitudinal age slopes.

To allow for different longitudinal slopes in IOP in age intervals < 30, 30–39, 40–49, 50–59, and ≥ 60 years, the above mixed model was extended with fixed-effects linear spline terms for age a_{ti} with knots at 30, 40, 50, and 60 years and constrained to be 0 at the overall mean age $\bar{a}$.[2] The homogeneity of longitudinal slopes across age intervals was contrasted by using Wald tests for the joint null hypothesis that all linear spline coefficients were

simultaneously zero. In addition, to display the smooth longitudinal trend in IOP with age, the mixed model was also extended with fixed-effects restricted quadratic spline terms for age a_{ti} with the same knots and centering described above.[2]

To evaluate potential heterogeneity of longitudinal age effects on IOP by sex, interactions of sex with the homogeneous linear term $a_{ti} - \overline{a}$, linear spline terms, and restricted quadratic spline terms were included as fixed effects in the corresponding mixed models. Age-by-sex interactions were contrasted by performing joint Wald tests for all interaction coefficients in each mixed model.

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CHAPTER 6

A LONGITUDINAL STUDY OF ASSOCIATION BETWEEN ADIPOSITY MARKERS AND INTRAOCULAR PRESSURE: THE KANGBUK SAMSUNG HEALTH STUDY

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ABSTRACT

Purpose: To examine the longitudinal and cross-sectional associations between body mass index (BMI), waist circumference, percent fat mass and intraocular pressure (IOP) in a large sample of Korean men and women.

Methods: We conducted a prospective cohort study of 274,064 young and middle age Korean adults with normal fundoscopic findings followed from January 1, 2002 to Feb 28, 2010. Health exams were scheduled annually or biennially. At each visit, IOP was measured in both eyes with automated noncontact tonometers. The longitudinal change in IOP with body mass index, waist circumference and percent fat mass was evaluated using three-level mixed models for longitudinal paired-eye data accounting for correlations between paired eyes and repeated measurements over time.

Results: In the fully adjusted models, the average longitudinal IOP increase for each interquartile change of BMI, waist circumference, and percent fat mass was 0.181mmHg (95% confidence interval [CI] 0.171 to 0.190), 0.269 mmHg (95% confidence interval [CI] 0.253 to 0.284) and 0.100 mmHg (95% confidence interval [CI] 0.090 to 0.110), respectively, with marked sex differences ($P < 0.001$). The average cross-sectional differences in baseline IOP per interquartile increase in baseline BMI, waist circumference and percent fat mass were 0.393 mmHg (95% CI 0.379 to 0.407), 0.434 mmHg (95% CI 0.412 to 0.456 mm Hg), and 0.428 mmHg (95% CI 0.410 to 0.445 mm Hg).

Conclusions: Adiposity was positively associated with increased IOP in a large cohort of Korean adults, and the association was evident in central obesity. Patients with elevated weight, or normal weight but excess central adiposity, could be identified and referred for eye screening. Further research is needed to better understand the underlying mechanisms of the

heterogeneous effects by sex, and to establish evidence of weight reduction in terms of reducing IOP.

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INTRODUCTION

Intraocular pressure (IOP) is a key risk factor in the development and progression of primary open-angle glaucoma[1], and IOP reduction or stabilization is the only proven method for glaucoma treatment.[2] IOP is a complex trait influenced by multiple risk factors. Identifying potentially modifiable risk factors for IOP is crucial to understand the pathophysiology of glaucoma and develop strategies accordingly that may prevent the onset or improve the prognosis of the disease.

Emerging evidences have suggested an association between elevated IOP and traditional cardiovascular (CVD) risk factors including age[3-8], hypertension[9-13] and diabetes[14-17]. Obesity or elevated body mass index (BMI), as a potential cause of hypertension and diabetes, have also shown independent positive associations with IOP in several cross-sectional[17-20] and longitudinal[5, 7, 21-25] studies. The cross-sectional studies could not establish the temporality of the association. And the previous longitudinal studies on the association between IOP and obesity were limited by small sample sizes, highly selective population, or short follow-up period. Another important weakness in the early cohort studies is the underdevelopment and usage of proper statistical methodology in assessing the longitudinal associations, resulting in inability to separate the cross-sectional with the longitudinal effects. In addition, no previous longitudinal study has assessed the association between central adiposity indicators (such as waist circumference and percent fat mass) with IOP levels. Central adiposity has been shown to be a better predictor of cardiovascular disease risk than BMI.[26] There are important clinical implications if body shape or composition is better predictors of the IOP trajectory, compared with traditional measure of relative weight.

The objective of this study is thus to evaluate the longitudinal association between changes in body adiposity markers (BMI, waist circumference and percent fat mass) and IOP over time in a cohort study of a large sample of healthy Korean men and women attending regular health screening visits.

METHODS

Study design and population

The Kangbuk Samsung Health Study is a longitudinal cohort study of 281,238 Korean men and women 18 years of age or older who underwent comprehensive annual or biennial screening health examinations at the two Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea.[27] Health exams were scheduled every 2 years for participants younger than 40 years of age and every year for participants 40 years of age or older from January 1, 2002, to February 28, 2010. Over 80% of the participants were employees of various companies or local government organizations and their spouses, who participated in annual or biennial health screening exams paid by employers under the Korean Industrial Safety and Health Law. The remaining participants voluntarily purchased self-paid screening exams at the health exam center.

The present analysis included 280,911 study participants (number of visits was 604,416) who underwent tonometry as part of the comprehensive health examination between January 1, 2002 and February 28, 2010. The following exclusion criteria were applied: visits after participants developed an absolute difference in IOP between both eyes greater than 6 mm Hg, as this is a marker of high risk of glaucoma (n=9,225 visits);[28] visits with missing fundus photograph (n=1,652 visits); visits after participants developed abnormal findings in fundus

photographs (n=15,458 visits). We further excluded participants with missing IOP measurements at all visits (n=100 visits). Thus, the final sample for this study included 274,064 participants (119,723 women and 154,341 men) free of eye disease with a total of 577,981 screening visits. The mean (SD) number of study visits per person was 2.2 (1.6).

This study was approved by the Institutional Ethics Committee of the Kangbuk Samsung Hospital. The requirement of informed consent was waived by the Ethics Committee as only de-identified data routinely collected during health screening visits were used.

Measurements

At each screening exam, IOP was measured with automated noncontact tonometers (2002–2004: TX-10, Canon, Tokyo, Japan; 2005–2008: TX-F, Topcon, Itabashi, Tokyo, Japan; 2009 onwards: CT-80, Topcon, Itabashi, Tokyo, Japan) in both eyes. Extreme IOP readings below 5 mm Hg (0.02%) or above 30 mm Hg (0.16%) were set to missing because of the potential for measurement error. The IOP measurement time was approximated as the time of registration at the exam center and classified into morning or afternoon. Fundus photographs were taken with a nonmydriatic fundus camera (CR6-45NM, Canon, Tokyo, Japan).

Height, weight, waist circumference and body composition were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest to the nearest 0.1 cm while subjects were standing with their weight equally distributed on both feet, their arms at their sides, and head facing straight forward. Waist circumference was measured only in participants attending the Seoul center (n = 184,579). Percent fat mass was

measured using a multi-frequency bioimpedance analyzer (Inbody 3.0 and inbody 720, Biospace Co., Seoul, Korea).

Demographic characteristics, smoking status, alcohol consumption, physical activity, medical history, and medication use were collected through standardized, self-administered questionnaires. Smoking status was categorized into never, former, or current smoking, frequency of current alcohol consumption was categorized into < 1, 1–3, or > 3 days/week, and frequency of vigorous physical activity was categorized into none, 1–3, or > 3 times/week. Sitting blood pressure and heart rate were measured by trained nurses. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, a self-reported history of hypertension, or current use of antihypertensive medications.

Blood specimens were sampled from the antecubital vein after at least 12 hours of fasting. Serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were described in detail elsewhere.[27] Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dL, a self-reported history of diabetes, or current use of antidiabetic medications.

Statistical analysis

We used several approaches to assess the longitudinal and cross-sectional associations between body adiposity markers and IOP. To control for the cross-sectional effect of baseline values while assessing the longitudinal associations between change in adiposity markers and IOP trajectory, the variables of baseline and change in adiposity markers were evaluated in the same model. We also accounted for the correlations in IOP measurements arising from both paired eyes and repeated measurements over time in the same participant. The main analyses consisted of three-level linear mixed models for longitudinal paired-eye data.[29, 30] Details of the

models are provided in the **Statistical Appendix**. Briefly, we modeled linear associations in IOP with baseline adiposity markers and change in adiposity markers from baseline for each eye at the first level, variations in IOP trajectories between both eyes of the same participant at the second level, and variations in IOP slopes across participants at the third level.

These mixed models provided the average cross-sectional difference in baseline IOP per 1 unit increase in baseline adiposity markers, as well as the average longitudinal change in IOP per 1 unit increase in change of adiposity markers, while they allowed for random variations in longitudinal changes among participants and between eyes within participants according to normal distributions with unstructured variance-covariance matrices.

To adjust for confounding and to evaluate potential mediating factors, we used three models with increasing degrees of adjustment. The first model adjusted for baseline age (continuous), change in age from baseline (continuous), sex (male or female) and study center (Seoul or Suwon). The second model further adjusted for potential confounding effects of height (continuous), as well as the baseline and time-varying changes in IOP measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), and physical activity (none, 1–3, or > 3 times/week). The third model further included potential mediators of the baseline and time-varying changes in hypertension (yes or no) and diabetes (yes or no).

To allow for nonlinear cross-sectional and longitudinal relationships, we extended the above mixed models with linear cross-sectional and longitudinal spline terms. For the cross-sectional association, we compared the baseline IOP across quartiles of the baseline adiposity markers with the first quartile; for the longitudinal association, we compared the longitudinal change of IOP by quartile indicators of change in adiposity markers with the baseline

(constrained to be 0). In addition, we assessed the smooth cross-sectional and longitudinal IOP associations with adiposity markers using a restricted quadratic spline function of the baseline and change in adiposity markers with knots at the 5th, 50th, and 95th percentiles. To evaluate potential heterogeneity of the association between IOP and adiposity by sex, interactions of sex and adiposity were included as fixed effects in the mixed models.

Additional analyses without excluding participants with abnormal fundoscopy findings or with between-eye differences in IOP greater than 6 mmHg (280,911 participants with 604,416 visits) were conducted. In addition, we performed a sensitivity analysis restricted to participants with two or more screening visits (130,991 participants with 435,262 visits). All reported *P* values were two-sided and the significance level was set at 0.05. Statistical analyses were undertaken using Stata (version 12; Stata Corp., College Station, Texas).

RESULTS

The mean (SD) BMI, waist circumference, percent fat mass, and IOP of study participants at baseline were 23.5 (3.2) kg/m^2, 79.8 (9.5) cm, 24.9 (6.4) % and 13.5 (2.7) mmHg, respectively (**Table 1**). Participants who had higher baseline IOP were generally older, higher, more likely to be males, smokers, alcohol drinkers, and had higher heart rate, blood pressures, cholesterol levels, fasting glucose, BMI, waist circumference and percent fat mass compared with participants with the lowest quartile of IOP levels.

Over the 8 year follow-up, the mean (SD) change in IOP from baseline was -0.12 (1.45). Longitudinally, IOP was positively associated with the changes in all body adiposity markers (**Table 2**). Adjusting for hypertension and diabetes as mediators (Model 3) did not substantially reduce the effect sizes. The median (interquartile range) in changes of BMI, waist circumference, and percent fat mass from baseline was 0.14 (-0.49, 0.77), 0.80 (-2.30, 3.90) and

0.29 (-1.39, 2.00), respectively. In the fully adjusted models, the average longitudinal IOP increase for each interquartile change of BMI, waist circumference, and percent fat mass was 0.181mmHg (95% confidence interval [CI] 0.171 to 0.190), 0.269 mmHg (95% confidence interval [CI] 0.253 to 0.284) and 0.100 mmHg (95% confidence interval [CI] 0.090 to 0.110), respectively. Compared with baseline values, IOP decreased with decreasing body adiposity levels. The positive longitudinal associations in IOP with change in body adiposity markers were also evident in restricted quadratic spline models, which showed a relatively marked slope for change in waist circumference and BMI, and a flatter slope for change in percent fat mass (**Figure 1**).

Cross-sectioinally, baseline IOP was also significantly positively associated with baseline adiposity markers, with a stronger effect than the longitudinal associations (**Supplementary Table 1 and Supplementary Figure 1**). After adjusting for hypertension and diabetes as mediators (Model 3), the effect size reduced but remained significant. The average cross-sectional differences in baseline IOP per interquartile increase in baseline BMI, waist circumference and percent fat mass were 0.393 mmHg (95% CI 0.379 to 0.407), 0.434 mmHg (95% CI 0.412 to 0.456 mm Hg), and 0.428 mmHg (95% CI 0.410 to 0.445 mm Hg).

Interestingly, the longitudinal associations between adiposity and IOP were somewhat stronger in men than in women while the cross-sectional associations were weaker in men than in women (**Figure 2**). Additional analyses without excluding participants with abnormal fundoscopy findings or with between-eye differences in IOP greater than 6 mmHg yielded similar results. Sensitivity analyses restricting the study population to participants with at least two screening visits did not materially affect the results (data not shown).

DISCUSSION

In this large cohort of Korean adults, IOP was positively associated with body mass index, waist circumference and percent fat mass both longitudinally and cross-sectionally. BMI and waist circumference were better longitudinal predictors for IOP vs. percent fat mass. The decrease in body adiposity levels had a greater impact on IOP reduction in men than women. The cross-sectional associations between body adiposity and IOP followed the same pattern but were more evident than the longitudinal associations. These associations were independent of conventional cardiovascular risk factors including hypertension and diabetes. This is also the first study that assessed the longitudinal associations between central obesity and IOP. The strength of our study include large sample size, the wide range in baseline and change of adiposity, the availability of repeated IOP measurements in both eyes in study participants, and the use of longitudinal analyses that controlled for the cross-sectional effects.

The positive association between IOP and BMI was also reported in other longitudinal studies conducted in Japan, China, and West Indies.[5, 7, 21-25] However, some limitations existed in previous studies that warrant the current analyses. The Beijing Eye study[22] and another Japanese study[24] had small sample size (2257 Chinese and 896 Japanese individuals) and had only two measurements 5 years apart. Two other studies in Japan[23, 25] and the Barbados Eye Study[7] mainly aimed at assessing the association between age, other systemic risk factors with IOP, and BMI was included as a covariate in the multivariate regression but not studied in depth. The other Japanese study found the positive association between slope of IOP with slope of BMI but did not estimate the relative magnitude of IOP change associated with absolute change in BMI.[21]

Several mechanisms may explain an increase in IOP with higher adiposity. The excessive intraobital adipose tissue may have an effect on increasing episcleral venous pressure,

thereby causing a rise in IOP as a consequence of impaired aqueous humor outflow facility.[31, 32] In addition, obesity-related diseases, such as high blood pressures and diabetes, may serve as mediators on the pathway between obesity and IOP. Increased blood pressure increased filtration of aqueous humor through elevated capillary pressure and reduced aqueous humor outflow through elevated episcleral venous pressure.[33] Hyperglycemia may induce an osmotic gradient that shifts excess aqueous humor into the anterior chamber.[34] Both can ultimately lead to elevated IOP. This is also supported by our results that the association between IOP and adiposity was weaker after adjusting for hypertension and diabetes. Obesity is also a risk factor for vascular endothelial dysfunction and autonomic dysfunction[35, 36], which are associated with abnormal ocular blood flow and perfusion instability. Furthermore, obesity-related oxidative stress may cause trabecular meshwork degeneration, impair the ability of the intracellular tissue to modulate outflow resistance, and results in IOP elevation.[37]

The impact of change in anthropometric parameters on IOP was stronger in waist circumference compared with BMI, suggesting that central adiposity, particularly a greater amount of intraabdominal or visceral fat, may be better predictor of risk of high IOP than the other anthropometric measures. On the other hand, the weaker change in IOP associated with percent fat mass may be due to the fact that the percent fat mass is a measurement of subcutaneous adiposity, but not indicative of fat distribution or visceral fat accumulation. This result suggested that patients with normal BMI but who are centrally obese are also at risk for high IOP and could be recommended to undergo routine screening for glaucoma.

Clear pathophysiological explanation for the gender differences of the association between IOP and adiposity is currently lacking. A possible reason is the difference in body fat distribution between men and women, as men have higher volume of visceral abdominal

adipose tissue than women.[38] Hormonal differences may explain the heterogeneity by sex.[39] Estrogen levels increase with increasing adipose, and may affect the inflow of aqueous humour, the ciliary body and the trabecular meshwork.[40, 41] Further research is needed to understand gender-related differences in IOP and adiposity.

Weight loss has been proven to be an effective strategy in reducing the risk for many health problems such as hypertension and diabetes, but it was not considered a standard approach in glaucoma treatments. In our study, weight loss was associated with IOP reduction over time, and therefore could potentially become a lifestyle or therapeutic intervention in lowering IOP, the objective in all current glaucoma treatments. Nevertheless, the effect of weight loss on IOP reduction and glaucoma prognosis has never been evaluated in clinical trials. Future clinical trials are needed to assess the role of weight management in IOP reduction among obese patients, or patients with normal-weight central obesity.

Our study has several strengths. First, the Kangbuk Samsung Health Study is by far the largest population-based cohort study evaluating the association between adiposity and IOP. Second, the longitudinal structure permitted us to evaluate within-person changes in IOP related with adiposity changes, avoiding biases commonly seen in cross-sectional studies. Third, the retaining of participants was fair (over 77% of participants recruited in the first year of the study had at least one additional follow-up visit). Fourth, besides BMI, repeated measurements of waist circumference and percent fat mass was also appraised, and we were able to incorporate multiple potential confounders and intermediate factors, allowing for a detailed characterization of the association between central obesity, subcutaneous adiposity and IOP. Finally, we used a statistical approach that controlled for baseline effect while obtaining the longitudinal association between adiposity change with change in IOP, based on a three-level

hierarchical approach to appropriately account for correlations between eyes and between visits for each participant.

Some limitations of our study also need to be considered. First, we used non-contact tonometers to measure IOP. This may have resulted in measurement error that may underestimate study associations compared with applanation tonometers, the gold standard. Second, our study included preferentially young and middle-age adults below 60 years of age, and only 6% of study participants were 60 years of age or over at baseline, which may limit our ability to make inference on the relationship of adiposity with IOP in elder populations. Finally, our study population consisted of apparently healthy middle-age Korean men and women attending health screening visits, which may limit the generalizability of our findings to other populations.

In conclusion, we found that excess adiposity was associated with significantly increased IOP in a large cohort of Korean adults attending health screening visits, an association that was stronger in central obesity. As a consequence, patients with elevated weight, or normal weight but excess central adiposity, could be identified and referred for eye screening. Further research is needed to better understand the underlying mechanisms of the heterogeneous effects by sex, and to establish evidence of weight reduction in terms of reducing IOP and delaying or preventing glaucoma complications.

Table 1. Participants' characteristics at baseline.*

Characteristic		Intraocular pressure†			
	Overall	Quartile 1 (<11.6 mmHg)	Quartile 2 (11.6-13.5 mmHg)	Quartile 3 (13.6-15.5 mmHg)	Quartile 4 (>15.5 mmHg)
Participants	274,136	71206	77036	68777	56503
Intraocular pressure†, mm Hg	13.5±2.7	10.3±1.0	12.8±0.6	14.7±0.6	17.4±1.4
Age, years	40.1±10.0	40.2±10.2	40.3±10.1	40.1±9.9	39.7±9.8
Male	153,964 (56.3)	31,521 (44.3)	42,788 (55.5)	43,042 (62.6)	36,613 (64.8)
Study center					
Seoul	184,579 (67.5)	47,876 (67.2)	53,146 (69.0)	47,838 (69.6)	35,719 (63.2)
Suwon	88,943 (32.5)	23,330 (32.8)	23,890 (31.0)	20,939 (30.4)	20,784 (36.8)
Smoking status					
Never	146,797 (54.7)	43,791 (62.7)	41,828 (55.3)	34,131 (50.5)	27,047 (48.7)
Former	45,385 (16.9)	9,833 (14.1)	12,828 (17.0)	12,378 (18.3)	10,346 (18.6)
Current	76,411 (28.4)	16,212 (23.2)	20,985 (27.7)	21,111 (31.2)	18,103 (32.6)
Alcohol drinking, days/week					
< 1	172,507 (64.0)	49,438 (70.4)	49,177 (64.7)	41,129 (60.6)	32,763 (58.8)
1–3	70,964 (26.3)	15,563 (22.2)	19,570 (25.8)	19,241 (28.4)	16,590 (29.8)
> 3	26,231 (9.7)	5,210 (7.4)	7,206 (9.5)	7,490 (11.0)	6,325 (11.4)
Physical activity, times/week					
0	147,395 (54.6)	39,622 (56.4)	41,546 (54.6)	36,368 (53.5)	29,859 (53.5)
1–3	77,858 (28.8)	18,736 (26.7)	21,950 (28.8)	20,377 (30.0)	16,795 (30.1)
> 3	44,899 (16.6)	11,937 (17.0)	12,620 (16.6)	11,223 (16.5)	9,119 (16.4)
Height, cm	166.1±8.6	165.2±8.4	166.1±8.6	166.7±8.6	166.7±8.6
Heart rate, beats/min	67.1±9.3	65.6±8.7	66.7±9.0	67.7±9.4	69.0±10.0
Body mass index, kg/m2	23.5±3.2	22.8±3.0	23.4±3.1	23.8±3.2	24.2±3.3
Waist circumference, cm	79.8±9.5	77.4±9.3	79.6±9.4	81.0±9.3	81.7±9.4
Percent fat mass, %	24.9±6.4	24.9±6.4	24.8±6.4	24.8±6.4	25.3±6.4
Diabetes	10,707 (3.9)	1,615 (2.3)	2,485 (3.2)	2,976 (4.3)	3,631 (6.4)
Fasting Glucose, mg/dL	95.2±16.8	92.5±12.5	94.5±15.2	96.2±17.4	98.7±21.6
Total cholesterol, mg/dL	194.6±35.2	189.8±34.2	193.8±34.8	196.4±35.2	199.7±36.1
HDL, mg/dL	55.3±12.4	56.2±12.8	55.4±12.4	54.9±12.2	54.5±12.1
LDL, mg/dL	112.4±29.8	108.8±29.0	111.8±29.5	113.8±29.8	116.3±30.5
Triglycerides, mg/dL	126.8±86.1	110.7±71.8	124.0±82.6	133.6±91.7	143.3±96.6
Hypertension	47,494 (17.4)	8,247 (11.6)	12,161 (15.8)	13,343 (19.4)	13,743 (24.3)
SBP, mm Hg	114.8±14.6	111.2±13.6	114.1±14.0	116.3±14.5	118.8±15.3
DBP mm Hg	74.3±10.0	71.8±9.5	73.9±9.8	75.4±10.0	76.9±10.4

* Data are means±SDs or number (%).

† Means (between-subject SDs) for the average intraocular pressure of left and right eyes overall and by age group at baseline.

Table 2. Longitudinal associations between intraocular pressure and change of adiposity markers

	Interval of change compared with baseline					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Interquartile range ‡	P value†
Change in BMI, kg/m^2						
No. of subjects/visits	45881/75937	54132/75938	54195/75937	45363/75937	130855/303749	
Median (range)	-1.00 (-11.35, -0.49)	-0.15 (-0.49, 0.14)	0.43 (0.14, 0.77)	1.26 (0.77, 11.76)	0.14 (-0.49, 0.77)	
Model 1§	-0.255 (-0.272, -0.238)	-0.097 (-0.113, -0.081)	-0.007 (-0.022, 0.009)	0.145 (0.127, 0.163)	0.203 (0.193, 0.212)	<0.001
Model 2‖	-0.214 (-0.232, -0.197)	-0.079 (-0.095, -0.062)	0.004 (-0.012, 0.020)	0.138 (0.120, 0.157)	0.181 (0.172, 0.191)	<0.001
Model 3¶	-0.212 (-0.230, -0.195)	-0.075 (-0.091, -0.059)	0.007 (-0.009, 0.023)	0.140 (0.122, 0.158)	0.181 (0.171, 0.190)	<0.001
Change in waist circumference, cm						
No. of subjects/visits	20431/30392	23123/30142	23139/30003	20619/30313	59459/120850	
Median (range)	-4.50 (-54.80, -2.30)	-0.70 (-2.30, 0.80)	2.20 (0.80, 3.90)	6.10 (3.90, 40.20)	0.80 (-2.30, 3.90)	
Model 1§	-0.381 (-0.408, -0.354)	-0.171 (-0.197, -0.146)	-0.037 (-0.062, -0.011)	0.120 (0.093, 0.146)	0.286 (0.271, 0.301)	<0.001
Model 2‖	-0.354 (-0.382, -0.327)	-0.160 (-0.186, -0.134)	-0.038 (-0.064, -0.012)	0.117 (0.090, 0.144)	0.270 (0.255, 0.285)	<0.001
Model 3¶	-0.352 (-0.380, -0.324)	-0.159 (-0.185, -0.133)	-0.037 (-0.063, -0.011)	0.118 (0.091, 0.145)	0.269 (0.253, 0.284)	<0.001
Change in percent fat mass, %						
No. of subjects/visits	42564/65369	47794/65369	47721/65368	42358/65369	117867/261475	
Median (range)	-2.70 (-60.47, -1.39)	-0.49 (-1.39, 0.29)	1.08 (0.29, 2.00)	3.35 (2.00, 31.56)	0.29 (-1.39, 2.00)	
Model 1§	-0.165 (-0.183, -0.147)	-0.080 (-0.097, -0.063)	-0.032 (-0.049, -0.014)	0.080 (0.061, 0.099)	0.126 (0.117, 0.136)	<0.001
Model 2‖	-0.122 (-0.141, -0.103)	-0.058 (-0.076, -0.040)	-0.021 (-0.039, -0.003)	0.072 (0.053, 0.092)	0.103 (0.093, 0.113)	<0.001
Model 3¶	-0.117 (-0.136, -0.098)	-0.054 (-0.071, -0.036)	-0.018 (-0.036, -0.001)	0.073 (0.053, 0.092)	0.100 (0.090, 0.110)	<0.001

* Obtained from linear mixed models with different intersecting linear trends in each quartile interval, and random variations in linear trends among participants and between eyes within participants.

‡ The average longitudinal changes and their 95% confidence intervals in intraocular pressure with interquartile change in body weight markers (1.26 kg/m^2 for BMI, 6.20 cm for waist circumference, 3.40% for percent fat mass, 3.21% for percent muscle mass)

† *P* value for homogeneity of annual changes across all quartile intervals.

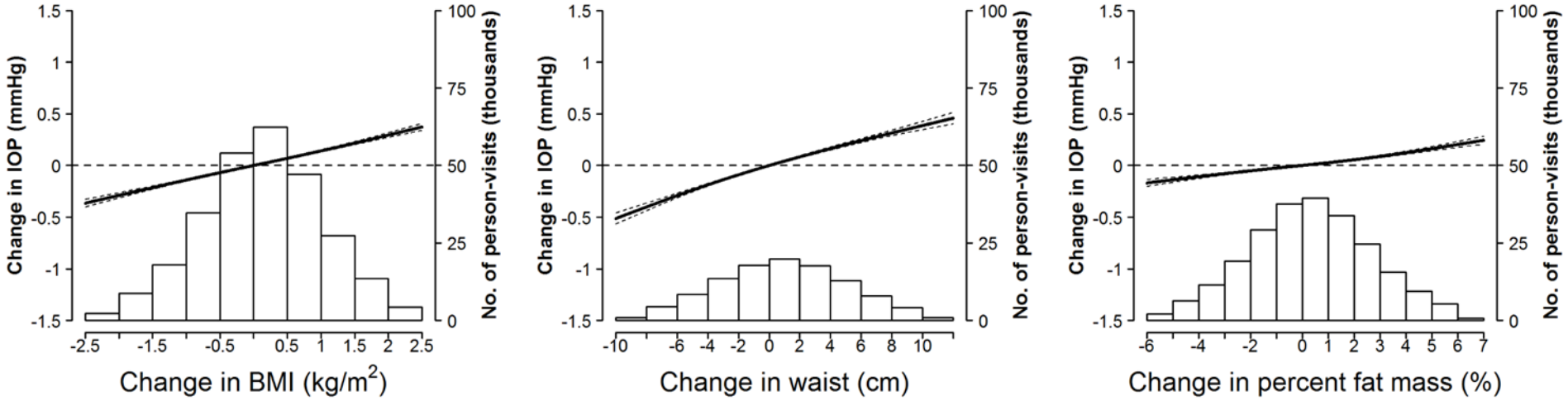
§ Adjusted for baseline age (continuous), change in age (continuous), sex (male or female), and study center (Seoul or Suwon).

‖ Further adjusted for height (continuous), baseline and time-varying changes in intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week) and heart rate (continuous).

¶ Further adjusted for baseline and time-varying changes in hypertension (no or yes) and diabetes (no or yes).

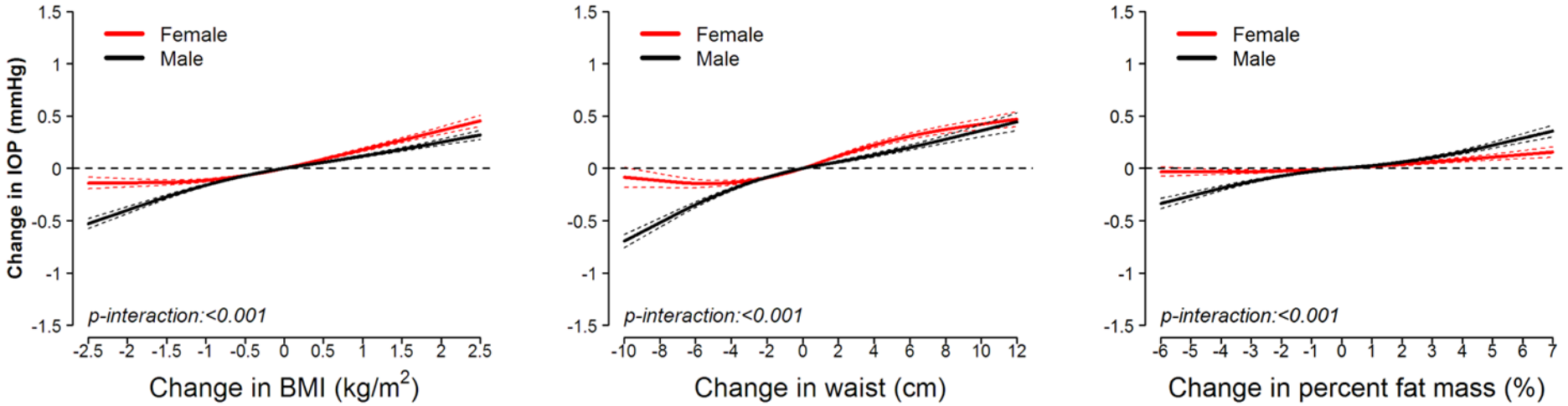
FIGURE LEGENDS

Figure 1. Longitudinal associations between intraocular pressure and change in body adiposity over time.



Curves represent adjusted average change in intraocular pressures (solid lines) and their 95% confidence intervals (dashed lines) based on restricted quadratic splines with knots at 5th, 50th and 95th percentile. Results were obtained from linear mixed models with random variations in IOP changes among participants and between eyes within participants, and adjusted for baseline adiposity marker levels (continuous), sex (male or female), study center (Seoul or Suwon), height (continuous), and baseline and time-varying changes in age(continuous), intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), hypertension (no or yes), and diabetes (no or yes). The histogram represents the body adiposity marker change distribution of person-visits among participants.

Figure 2. Longitudinal associations between intraocular pressure and change in body adiposity over time, by sex.



Curves represent adjusted average change in intraocular pressures (solid lines) and their 95% confidence intervals (dashed lines) based on restricted quadratic splines with knots at 5th, 50th and 95th percentile. Results were obtained from linear mixed models with interactions between spline terms and sex, random variations in IOP trends among participants and between eyes within participants, and adjusted for baseline adiposity marker levels (continuous), sex (male or female), study center (Seoul or Suwon), height (continuous), and baseline and time-varying changes in age(continuous), intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), hypertension (no or yes), and diabetes (no or yes).

Supplemental Table 1. Cross-sectional associations between intraocular pressure and baseline body adiposity

	Baseline intervals compared with 1st quartile					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Interquartile range ‡	P value†
Baseline BMI, kg/m^2						
No. of subjects	68513	68508	68510	68510	274041	
Median (range)	19.93 (13.66, 21.27)	22.37 (21.27, 23.37)	24.37 (23.37, 25.51)	27.07 (25.51, 61.44)	23.37 (21.27, 25.51)	
Model 1§	Reference	0.275 (0.248, 0.303)	0.533 (0.504, 0.561)	0.951 (0.922, 0.980)	0.509 (0.496, 0.523)	<0.001
Model 2‖	Reference	0.257 (0.230, 0.284)	0.490 (0.462, 0.518)	0.860 (0.831, 0.889)	0.458 (0.444, 0.472)	<0.001
Model 3¶	Reference	0.249 (0.222, 0.276)	0.452 (0.424, 0.480)	0.744 (0.715, 0.774)	0.393 (0.379, 0.407)	<0.001
Baseline waist circumference, cm						
No. of subjects	42421	39421	38225	39821	159888	
Median (range)	68.60 (36.00, 73.00)	77.00 (73.10, 80.00)	83.20 (80.10, 86.40)	90.80 (86.50, 142.00)	80.00 (73.00, 86.40)	
Model 1§	Reference	0.392 (0.356, 0.427)	0.640 (0.600, 0.679)	0.902 (0.861, 0.943)	0.519 (0.498, 0.540)	<0.001
Model 2‖	Reference	0.381 (0.345, 0.417)	0.616 (0.576, 0.656)	0.885 (0.843, 0.927)	0.511 (0.490, 0.533)	<0.001
Model 3¶	Reference	0.362 (0.326, 0.398)	0.557 (0.517, 0.596)	0.754 (0.712, 0.796)	0.434 (0.412, 0.456)	<0.001
Baseline percent fat mass, %						
No. of subjects	63768	63764	63758	63760	255050	
Median (range)	17.79 (1.25, 20.44)	22.49 (20.44, 24.46)	26.61 (24.46, 29.25)	32.57 (29.25, 78.52)	24.46 (20.44, 29.25)	
Model 1§	Reference	0.341 (0.313, 0.369)	0.569 (0.540, 0.599)	1.024 (0.990, 1.057)	0.605 (0.588, 0.622)	<0.001
Model 2‖	Reference	0.274 (0.246, 0.302)	0.446 (0.416, 0.475)	0.825 (0.790, 0.859)	0.497 (0.479, 0.514)	<0.001
Model 3¶	Reference	0.226 (0.198, 0.254)	0.365 (0.335, 0.395)	0.703 (0.669, 0.738)	0.428 (0.410, 0.445)	<0.001

* Obtained from linear mixed models with different intersecting linear trends in each quartile interval, and random variations in linear trends among participants and between eyes within participants.

‡ The average longitudinal changes and their 95% confidence intervals in intraocular pressure with interquartile change in body weight markers (4.24 kg/m^2 for BMI, 13.40 cm for waist circumference, 8.81% for percent fat mass, 8.53% for percent muscle mass)

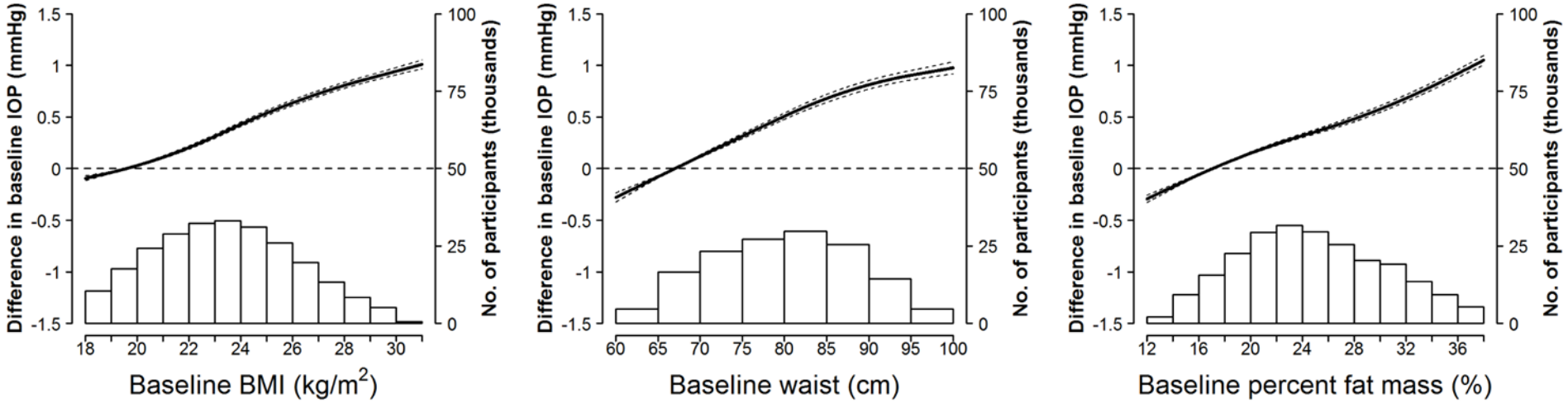
† *P* value for homogeneity of annual changes across all quartile intervals.

§ Adjusted for baseline age (continuous), change in age (continuous), sex (male or female), study center (Seoul or Suwon).

‖ Further adjusted for height (continuous), baseline and time-varying changes in intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week) and heart rate (continuous).

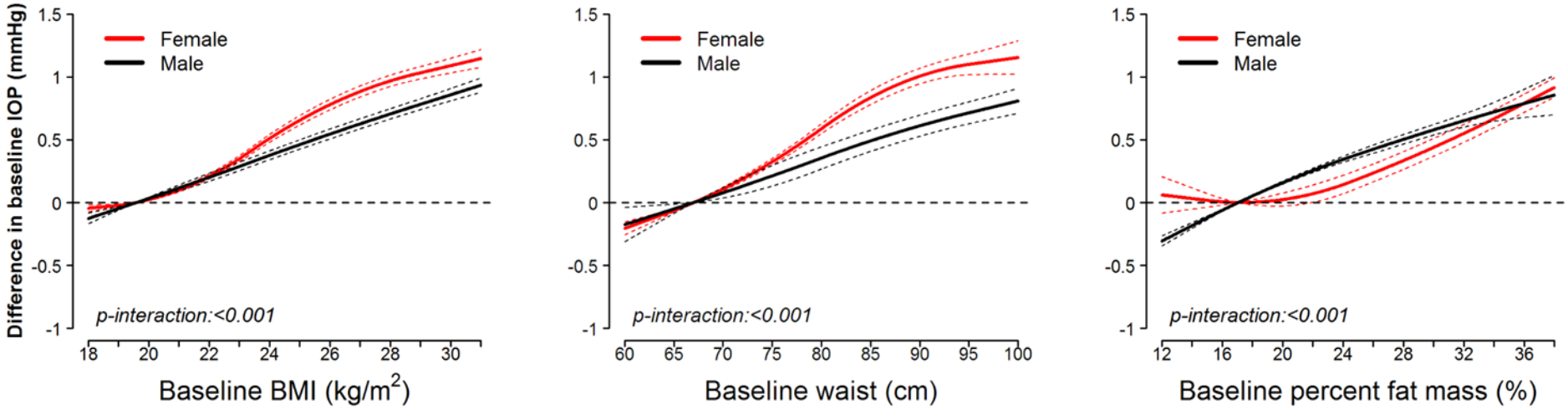
¶ Further adjusted for baseline and time-varying changes in hypertension (no or yes) and diabetes (no or yes).

Supplemental Figure 1. Cross-sectional associations between baseline intraocular pressure and baseline body adiposity



Curves represent adjusted difference in baseline intraocular pressures (solid lines) and their 95% confidence intervals (dashed lines) across spectrum of baseline body adiposity marker levels compared with the 10th percentile based on restricted quadratic splines with knots at 5th, 50th and 95th percentile. Results were obtained from linear mixed models with random variations in IOP among participants and between eyes within participants, and adjusted for sex (male or female), study center (Seoul or Suwon), height (continuous), time-varying changes in adiposity markers (continuous), and baseline and time-varying changes in age(continuous), intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), hypertension (no or yes), and diabetes (no or yes). The histogram represents the frequency distribution of baseline body adiposity marker levels.

Supplemental Figure 2. Cross-sectional associations between baseline intraocular pressure and baseline body adiposity, by sex



Curves represent adjusted difference in baseline intraocular pressures (solid lines) and their 95% confidence intervals (dashed lines) across spectrum of baseline body adiposity marker levels compared with the 10th percentile based on restricted quadratic splines with knots at 5th, 50th and 95th percentile. Results were obtained from linear mixed models with interactions between spline terms and sex, random variations in IOP among participants and between eyes within participants, and adjusted for sex (male or female), study center (Seoul or Suwon), height (continuous), time-varying changes in adiposity markers (continuous), and baseline and time-varying changes in age(continuous), intraocular pressure measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), hypertension (no or yes), and diabetes (no or yes)

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STATISTICAL APPENDIX

Cross-sectional and longitudinal associations of body adiposity markers with intraocular pressure

To assess the cross-sectional association of body adiposity markers with intraocular pressure (IOP) at baseline, as well as the longitudinal association between changes in adiposity markers (body mass index, waist circumference, percent fat mass) and IOP over time, we developed linear mixed models for longitudinal paired-eye data using a three-level hierarchical approach.[1, 2] At the first within-eye level, the change in IOP levels Yijt from baseline visit t = 0 to follow-up visits t = 1,…, mi for eye j = 1, 2 of participant i = 1,…, n was related to the corresponding changes in the adiposity marker x_{it} and other subject-specific time-varying covariates z_{it} through the linear model

$$Y_{ijt} = \alpha_{ij0} + \alpha_{ij1}(x_{it} - x_{i0}) + \boldsymbol{\alpha}'_{ij2}(\mathbf{z}_{it} - \mathbf{z}_{i0}) + \varepsilon_{ijt},$$

where α_{ij0} was the expected baseline IOP for eye *j* of participant *i*; α_{ij1} was the expected change in IOP over time for eye *j* of participant *i* per unit change in the adiposity marker; $\boldsymbol{\alpha}_{ij2}$ were the expected longitudinal IOP slopes for that eye associated with the other time-varying covariates, including age (continuous), IOP measurement time (morning or afternoon), smoking status (never, former, or current), alcohol drinking (< 1, 1–3, or > 3 days/week), physical activity (none, 1–3, or > 3 times/week), heart rate (continuous), hypertension (yes or no) and diabetes (yes or no); and the within-eye errors ε_{ijt} were assumed to be independent and normally distributed with mean 0 and constant variance σ^2.

The second level represented the variation in coefficients α_{ij0}, α_{ij1}, and $\boldsymbol{\alpha}_{ij2}$ between eyes of the same participant. The eye-specific baseline IOP α_{ij0} was allowed to vary randomly

between each participant's eyes, whereas the longitudinal IOP slopes for the adiposity marker α_{ij1} and the other time-varying covariates $\boldsymbol{\alpha}_{ij2}$ were assumed to be fixed for both eyes. Thus, the second-level model was

$$\alpha_{ij0} = \gamma_{i00} + b_{ij0},$$

$$\alpha_{ij1} = \gamma_{i10},$$

$$\boldsymbol{\alpha}_{ij2} = \boldsymbol{\gamma}_{i20},$$

where the between-eye variations within a subject b_{ij0} were assumed to be independent and normally distributed with mean 0 and constant variance τ^2. The longitudinal slopes associated with body adiposity markers α_{ij1} were specified as fixed at eye level because preliminary analyses showed virtually null random variation in longitudinal IOP slopes between each participant's eyes.

Finally, the third level described the variation in parameters γ_{i00}, γ_{i10}, and $\boldsymbol{\gamma}_{i20}$ across participants. The subject-specific baseline IOP γ_{i00} was linearly related to each participant's baseline levels of the adiposity marker x_{i0} and time-varying covariates $\mathbf{z}_{i0}$, as well as to other time-constant covariates $\mathbf{w}_i$, including sex (female or male), study center (Seoul or Suwon), and height (continuous). The subject-specific longitudinal IOP slopes for the adiposity marker γ_{i10} were allowed to vary randomly across participants, while the longitudinal slopes for the other time-varying covariates $\boldsymbol{\gamma}_{i20}$ were assumed to be constant for all participants. Specifically, the third-level model was

$$\gamma_{i00} = \beta_{000} + \beta_{001}x_{i0} + \boldsymbol{\beta}'_{002}\mathbf{z}_{i0} + \boldsymbol{\beta}'_{003}\mathbf{w}_i + b_{i00},$$

$$\gamma_{i10} = \beta_{100} + b_{i10},$$

$$\boldsymbol{\gamma}_{i20} = \boldsymbol{\beta}_{200},$$

where the between-subject variations b_{i00} and b_{i10} were assumed to follow a bivariate normal distribution with mean $\mathbf{0}$ and constant variance-covariance matrix $\mathbf{V}$. Combining the three nested models, we obtained the linear mixed model

$$Y_{ijt} = (\beta_{000} + b_{i00} + b_{ij0}) + \beta_{001}x_{i0} + \boldsymbol{\beta}'_{002}\mathbf{z}_{i0} + \boldsymbol{\beta}'_{003}\mathbf{w}_i$$
$$+ (\beta_{100} + b_{i10})(x_{it} - x_{i0}) + \boldsymbol{\beta}'_{200}(\mathbf{z}_{it} - \mathbf{z}_{i0}) + \varepsilon_{ijt},$$

which included two nested random effects for the intercept, as well as a random effect at subject level for the longitudinal slope associated with the adiposity marker, to account for correlations arising from both paired-eye data and repeated measurements over time.[3]

In this mixed model, the first line on the right-hand side represented the cross-sectional association of the adiposity marker with IOP at baseline. In particular, the fixed effect β_{001} corresponded to the mean difference in baseline IOP per unit increase in the baseline adiposity marker adjusted for baseline covariates. To allow for nonlinear cross-sectional relationships, we modified the fixed-effects specification for x_{i0} to compare the mean baseline IOP across quartiles of the baseline adiposity marker, as well as to estimate smooth baseline IOP changes as a restricted quadratic spline function of the baseline adiposity marker with knots at the 5th, 50th, and 95th percentiles.[4]

The second line of the above linear mixed model represented the longitudinal association of within-subject changes in the adiposity marker and IOP over time.[5] Specifically, the fixed effect β_{100} corresponded to the mean change in IOP over time per unit increase in the within-subject adiposity marker adjusted for baseline and time-varying covariates. To assess nonlinear longitudinal effects, we alternately replaced the linear term $x_{it} - x_{i0}$ in the above model with quartile indicators and restricted quadratic splines for within-subject changes in the adiposity marker with knots at the 5th, 50th, and 95th percentiles and constrained to be 0 at

baseline. Quartile indicators and linear spline terms were specified as random at subject level to allow for random between-subject variations around the average nonlinear longitudinal trend.

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CHAPTER 7

CONCLUSIONS

SUMMARY OF FINDINGS

Studies on the association of cardiovascular risk factors with IOP and POAG have been profuse but inconsistent. Diabetes, for instance, has been proposed as a risk factor for elevated IOP, but the association between diabetes mellitus and glaucoma is still controversial. [1–4] A meta-analysis published in 2004 concluded that diabetes mellitus was positively associated with glaucoma.[5] However, this meta-analysis was based only on cross-sectional or case-control studies bud didn't include longitudinal prospective studies and therefore subject to temporality bias. Similarly, the literature on the association between BP and POAG is limited and inconsistent.[2,6–8] Qualitative reviews have summarized the evidence on BP, IOP and glaucoma,[9–11] but quantitative estimates of the associations were lacking.

The association between age and IOP is also debatable subject. Cross-sectional and longitudinal studies have shown that IOP increases with age in Western populations.[12–15] On the contrary, cross-sectional studies in the Asian populations reported an inverse association between age and IOP,[16,17] while one longitudinal study in Japan arrive at an opposite conclusion.[18] The inconsistencies of these studies could be due to limited sample sizes or to methodological issues related to the analysis of the longitudinal IOP trajectories.

This dissertation adds to the ophthalmologic evidence by 1) systematically and quantitatively synthesize available literature on the association of high blood pressure, diabetes with IOP and POAG in the general populations; 2) Evaluating the influence of age on IOP in a longitudinal cohort study with a large sample of Korean adults; and 3) Evaluating the association between baseline and change in body adiposity with the baseline and change in IOP in the longitudinal cohort study.

In the first chapter, we conducted a systematic review of the available literature on the association between blood pressure levels and hypertension with primary open-angle glaucoma and intraocular pressure endpoints. Based on the sixty observational studies included in the final meta-analysis, we found consistent association between high blood pressure with increased IOP and higher risk of POAG. The pooled relative risk for primary open-angle glaucoma comparing patients with hypertension to those without hypertension was 1.16 (95% CI= 1.05-1.28), with modest heterogeneity across studies (I^2 34.5%). Virtually all studies reported a positive association between blood pressure and intraocular pressure. The pooled average increase in IOP associated with a 10 mmHg increase in SBP was 0.26 mmHg (95% CI 0.23 – 0.28, I^2 30.7%), and the average increase associated with a 5 mmHg increase in DBP was 0.17 mmHg (95% CI 0.11 – 0.23, I^2 90.5%).

In the second chapter, we conducted another systematic review of the available literature on the association of diabetes and blood glucose levels with glaucoma, intraocular pressure (IOP) and ocular hypertension in the general population. We found that diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP. The pooled relative risk for glaucoma comparing patients with to those without diabetes was 1.48 (95% CI 1.29 – 1.71), with significant heterogeneity across studies (I^2 82.3%, $p < 0.001$). The risk of glaucoma increased by 5% (95% CI 1 – 9%) for each year since diabetes diagnosis. The pooled average difference in IOP comparing patients with to those without diabetes was 0.18 mm Hg (95% CI 0.09 – 0.27, I^2 73.2%), while the pooled average increase in IOP associated with an increase in 10 mg/dL in fasting glucose was 0.09 mm Hg (95% CI 0.05 – 0.12, I^2 34.8%).

In the third chapter, we conducted a cross-sectional analysis of 3,299 adults from 2005-2008 NHANES, to investigated the association between diabetes, pre-diabetes, metabolic syndrome and its components and the levels of fasting glucose, HbA1c and HOMA-IR with the prevalence of glaucoma. We found that diabetes was strongly associated with prevalent glaucoma. In fully adjusted models, the odds ratio for glaucoma comparing participants with diabetes with participants in the reference group with neither pre-diabetes nor diabetes was 2.12 (95% CI: 1.23, 3.67). The corresponding odd ratio comparing participants with pre-diabetes to those in the reference group was 1.01 (95% CI: 0.57, 1.82). Finally, patients with 5 or more years of diabetes duration had an OR for glaucoma of 3.90 (95% CI: 1.63, 9.32) compared with patients with <5 years of diabetes duration.

In the fourth chapter, we examined the longitudinal association between age and IOP in a prospective cohort study of 274,064 adult men and women who underwent a screening examination between January 2011 and December 2013 at the Kangbuk Samsung Total Healthcare Center in Seoul and Suwon, South Korea. The average longitudinal change in IOP per one-year increase in age was -0.066 mm Hg (95% CI -0.068 to -0.063), with marked sex differences ($P < 0.001$). In men, the average annual IOP change was -0.094 mm Hg (95% CI -0.096 to -0.091) throughout follow-up. In women, the average annual IOP change was -0.006 mm Hg (95% CI -0.010 to -0.003), with a relatively flat association in the middle-age range of 30–59 years and more marked annual decreases at younger and older ages.

In the fifth chapter, we examine the longitudinal and cross-sectional associations between body mass index (BMI), waist circumference, percent fat mass and IOP in Korean adults who participated in annual or biannual health examinations. The average longitudinal IOP increase for each interquartile change of BMI, waist circumference, and percent fat mass

was 0.181mmHg (95% confidence interval [CI] 0.171 to 0.190), 0.269 mmHg (95% confidence interval [CI] 0.253 to 0.284) and 0.100 mmHg (95% confidence interval [CI] 0.090 to 0.110), respectively, with marked sex differences ($P < 0.001$). In addition, the average cross-sectional differences in baseline IOP per interquartile increase in baseline BMI, waist circumference and percent fat mass were 0.393 mmHg (95% CI 0.379 to 0.407), 0.434 mmHg (95% CI 0.412 to 0.456 mm Hg), and 0.428 mmHg (95% CI 0.410 to 0.445 mm Hg).

IMPLICATIONS AND FUTURE RESEARCH

Our research suggested a consistent and robust association between blood pressure and IOP. A significant association between hypertension and POAG was also identified, although there was significant heterogeneity across study designs. In addition, diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of POAG, and that diabetes and fasting glucose levels were associated with increased levels of IOP. Our study also indicated that in a large cohort of Korean adults, IOP decreased with age but the decline was stronger in men compared with women and in participants <30 years of age compared with older participants. Furthermore, in this population, excess adiposity was associated with significantly increased IOP, independent of conventional cardiovascular risk factors including hypertension and diabetes. The decrease in body adiposity levels had a greater impact on IOP reduction in men than women, and BMI and waist circumference were better longitudinal predictors for IOP vs. percent fat mass.

These findings added to the growing body of evidence suggesting that cardiovascular disease risk factors may be important determinants for elevated IOP and glaucoma. Hypertensive and diabetic patients should be screened for elevated IOP and higher risk for POAG, and that hypertension management be included as part of POAG treatment regimes.

Additional prospective studies are needed to firmly establish the role of blood pressure in glaucoma development. There was a relative lack of research on the association between glucose biomarkers, prediabetes and metabolic syndrome with glaucoma. Given the high prevalence of these metabolic abnormalities, future studies should target this area of research to fully understand the implications of altered glucose metabolism on glaucoma risk. In addition, patients with elevated weight, or normal weight but excess central adiposity, could be identified and referred for eye screening. Clinical trials are needed to establish the role of weight management in IOP reduction among obese patients, or patients with normal-weight central obesity. Additional research could also aimed at better understanding heterogeneous effects by sex, the underlying mechanisms between cardiovascular risk factors with IOP and POAG, and to reconsider cutoffs for defining high IOP by age and sex groups in Asian populations.

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ACADEMIC EXPERIENCE

2011/08-Now Ph.D., Johns Hopkins University School of Public Health, Baltimore, MD

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2009/08-2011/06 M.H.S., Johns Hopkins University School of Public Health, Baltimore, MD

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2004/08-2009/07 B.A., Peking University, Beijing, China

- Major in Bio-medical English, Health Science Center

2005/09-2007/07 B.A., Peking University, Beijing, China

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2008/06-2008/08 Peking University Graduate School, Population Institute, Beijing, China

- Summer Class, Certificate of Social Science Research Design and Method

RESEARCH EXPERIENCE

2011/02-2014/02 Research Assistant, Department of Epidemiology and Welch Center for Prevention, Johns Hopkins University, Baltimore, MD

- Conducted analyses on estimating the risk factors associated with intraocular pressure in a large sample of Korean adults from Kangbuk Samsung Cohort Study.
- Assisted in proposal and protocol design, data cleaning and management.
- Participated in the development of linear mixed models for longitudinal paired-eye data using a three-level hierarchical approach.
- Synthesized issues and presented results to senior statisticians and ophthalmologists and inform the development of sophisticated overarching model.

2013/08-2013/08 Research Assistant, Kangbuk Samsung Medical Center, Seoul, Korea

- Performed statistical analyses for a cohort study on social stigma of cancer patients

2011/02-2012/02 Research Assistant, General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD

- Assisted in systematic review and meta-analysis for eligible clinical trials.
- Abstracted information from articles, perform quality and quantity synthesis.
- Used Microsoft Access to construct database for question forms.

2010/04-2011/01 Data Coordinator, Center for the Analysis and Management of MACS, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Assisted in Multicenter AIDS Cohort Study (MACS). Performed statistical and exploratory analysis using SAS.
- Cooperated with project investigators, responded to data requests, organized and compile raw data from multiple databases.
- Analyzed frequency distributions to revise semi-annual data collection forms, designed screening mechanisms for possible wrong responses, composed tables/figures for annual MACS report.
- Attended staff meetings and SAS programmer meetings for presentation and discussion of procedural issues, statistical topics, and review of analytical projects, methods and problems.

2010/03-2010/08 Research Assistant, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Assisted in Environmental Health Science Department for the relationship between food factors and the US counties' capability to cope with disasters.
- Obtained US counties' demographic and food-related variables from the United States Department of Agriculture and National Association of Counties county database.
- Employed iterative factor analysis algorithm to determine factors.
- Carried out principal components and cluster analysis.
- Summarized food factors: availability, accessibility, affordability, security and consumption according to their Cronbach's alpha coefficient.

2008/12-2009/04 Biostatistician, Cardiovascular Disease Sector, CDC, China, Beijing, China

- Did safety analysis of clinical trials using EPIDATA and SPSS.
- Constructed and managed database on which analytical model was built.
- Took part in prospective urban and rural population health research project.
- Searched and reviewed literatures.
- Designed Proposals and protocols.
- Translated epidemiology dissertations.

PROFESSIONAL EXPERIENCE

2009/04-2009/07 Project Assistant, Bain & Company, Beijing, China

- Assisted director in consultancy of an American pharmaceutical company's entry into the Chinese market.
- Conducted telephone interviews of leaders in drug companies or hospitals.
- Performed data searches for legislation and law about expanding branches in China.

2008/02-2008/07 Medical Intern, Beijing Shougang Hospital, Beijing, China

- Communicated with patients, wrote patients' medical records.
- Observed surgical operations in various departments, learned courses such as Internal Medicine, Gynecology & Obstetrics, and Surgery based on practice.

2008/10-2008/12 Marketing Intern, Motorola Enterprise Mobility business, Beijing, China

- Responsible for work prior to release of new products such as bar code scanner, wireless network card and mobile data terminal.
- Coordinated communication between suppliers and retailers.
- Organized release conference and prepared gifts with designing company. Discussed advertisements with magazine editors.

2008/07-2008/09 English Customer Service, China Mobile Customer Service Center, Beijing, China

- Offered information related to Olympic Games such as competition results and schedules.
- Assisted in communications between Chinese and foreigners.
- Provided professional China Mobile services such as weather report, traffic condition, hotel reservation, voice mailbox and resort recommendations.

2008/03-2008/08 Researcher, Beijing New-oriental School, Beijing, China

- Performed research and conducted questionnaires on competitive schools.
- Searched for information on clients and did stratification. Wrote reports for classes' markets based on statistics collected from New-oriental School and peer schools.
- Presented ideas on popularizing certain courses and improving class design.

2007/07-2007/10 Assistant Consultant, All China Marketing Research Co., Ltd. (ACMR), Beijing, China

- Worked in a partnership program between ACMR and IBISWorld.
- Assisted senior consultants in the company and from IBISWorld to complete reports which describe and analyze artificial limb, organ and implant equipment manufacturing in China.
- Worked well in teams and successfully interviewed management teams of medical companies by telephone.

PRESENTATION AND CONFERENCE PAPER

1. Donath E, Zhang L, Wright L, **Zhao D**, Galvagno S. Prevention of Atrial Fibrillation with Angiotension-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers-A Meta-Analysis. The 12th Annual ACCM Research Day, Baltimore, MD, December 2010.

PUBLICATION (PEER REVIEWED)

1. Kim MH, **Zhao D**, Kim W, Lim D-H, Song Y-M, Guallar E, Cho J, Sung J, Chung E-S, Chung T-Y. Heritability of myopia and ocular biometrics in Koreans: The Healthy Twin Study. *Invest Ophthalmol Vis Sci* 2013. Epub 2013 Apr 25.
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5. Zhang Y, Kim BK, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, Kwon MJ, Rampal S, **Zhao D**, Pastor-Barriuso R, Lima JA, Shin H, Guallar E. Thyroid Hormones and Coronary Artery Calcification in Euthyroid Men and Women. *Arterioscler Thromb Vasc Biol*. 2014. Epub 2014 Jul 24. [Pubmed] PMID: 25060795

WORKING PAPER (IN PROGRESS)

1. Cho J, **Zhao D,** Pastor-Barriuso R, Chang Y, Ryu S, Yoon KE, Zhang Y, Rampal S, Han WK, Shin HC, Guallar E**.** Changes in anthropometric measures and body composition before and after diabetes development: the Kangbuk Samsung Health Study.
2. **Zhao D**, Cho J, Kim MH, Guallar E**.** Diabetes, metabolic syndrome, and the risk of glaucoma: a meta-analysis (submitted).
3. **Zhao D**, Kim MH, Pastor-Barriuso R, Chang Y, Ryu S, Zhang Y, Rampal S, Shin H, Friedman D, Guallar E, Cho J,. A longitudinal study of age-related changes in intraocular pressure: the Kangbuk Samsung Health Study (submitted).
4. **Zhao D**, Cho J, Kim MH, Guallar E. Diabetes, glucose metabolism, and glaucoma: The Third National Health and Nutrition Examination Survey (submitted).
5. **Zhao D**, Kim MH, Pastor-Barriuso R, Chang Y, Ryu S, Zhang Y, Rampal S, Shin H, Guallar E, Cho J, ric acid and Coronary Artery Calcification in Asymptomatic Men and Women.
6. Kim MH, **Zhao D**, Cho J, Guallar E. Cadmium Exposure and Age-related Macular Degeneration (submitted)
7. Rebeccah McKibben, **Di Zhao**, Pamela L. Lutsey, Andrea L.C. Schneider, Eliseo Guallar, Thomas Mosley, and Erin D. Michos. Change in vitamin D status over 3-years and 10-years of follow-up: the Atherosclerosis Risk in Communities (ARIC) study.
8. Radhika Takiar, Pamela L. Lutsey, **Di Zhao**, Eliseo Guallar, Andrea L.C. Schneider, Morgan Grams, Lawrence Appel, Elizabeth Selvin, Erin D. Michos. 25-hydroxyvitamin D levels, vitamin D binding protein gene polymorphisms, and vitamin D3 epimer with risk of incident fracture-related hospitalization: Twenty-year follow up in a bi-ethnic cohort (the ARIC Study).

TEACHING

- 2011-2012 Teaching Assistant, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology 340.751 Epidemiologic Methods 1
- 2009-2010 Teaching Assistant, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology 550.694 Fundamentals Of Epidemiology

HONOR AND AWARDS

- Peking University Scholarship 2004-2005, Third Prize.
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- 2010/09-Present Information Chair (2010), Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health.
- 2009/10 ESO-ERICA Health Education Workshops. Provided health education workshops for immigrants and refugees.
- 2008/06 Volunteer for helping people suffering from the earthquake in Sichuan Province, China.
- 2008/03 Interpreter for The China and Global Health in the 21st Century Lancet Series Launch and workshop, hosted by China Medical Board, The Lancet and Peking University.
- 2007/12 Volunteer for Peking University Environmental Protection Union, recycling waste products for money to support impoverished children to go back to school.
- 2006/05 Organized International Conference *"Aging and Multifaceted aspects of Aging Diseases"*.
- 2005/11 Interpreter for the *2008 China Medical Board Presidents Council Meeting*.
- 2005/09 Peking University Student Union Social Practice Department.
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- Programming SAS, Stata, R, SQL, Oracle, Java, UNIX
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